**The Clinical and Cost-Effectiveness of Inotuzumab Ozogamicin for the Treatment of Adult Relapsed or Refractory B-cell Acute Lymphoblastic Leukaemia: an Evidence Review Group Evaluation of a NICE Single Technology Appraisal**

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**Abstract**

The National Institute for Health and Care Excellence (NICE) invited Pfizer, the manufacturer of inotuzumab ozogamacin (henceforth inotuzumab), to submit clinical and cost-effectiveness evidence for inotuzumab, as part of NICE’s Single Technology Appraisal process. The Centre for Reviews and Dissemination and Centre for Health Economics at the University of York were commissioned as the independent Evidence Review Group (ERG). The clinical effectiveness data were from a multicentre randomised controlled trial which compared inotuzumab to standard of care (SoC), where SoC was the investigator’s choice of chemotherapy. Inotuzumab demonstrated statistically significant improvements in the rates of response or in the proportion of patients progressing to haematopoietic stem cell transplant (HSCT), but failed to meet the second primary objective of longer overall survival. Treatment-emergent adverse events were more frequent in the SoC arm with the exception of veno-occlusive disease which was more frequent in the inotuzumab arm. The company’s economic model split patients into three post-hoc subgroups and used a partitioned survival approach within each group with a cure assumption three years after receipt of HSCT. In contrast to the trial results, the economic model estimated substantial improvement in survival with inotuzumab compared to SoC, providing an additional 5.2 life years and 2.2 quality-adjusted life years (QALYs) using a discount rate of 1.5% per annum. The ERG’s critique highlighted a number of concerns, including: the use of a post-hoc post-randomisation patient subset for extrapolation; the choice of a 1.5% discount rate; the complexity of the parametric modelling; the assumption of further treatment benefit post-HSCT; the nature of the cure assumption; and the length of inpatient stay during receipt of treatment. The combination of the ERG’s adjustments resulted in an incremental cost-effectiveness ratio (ICER) of £122,174 per QALY gained using Kaplan-Meier survival estimates, and £114,078 per QALY gained with parametric survival models fit to the trial data. The final determination of the appraisal followed four NICE Appraisal Committee meetings, an appeal by the company and other stakeholders, two patient access schemes and a company response to each appraisal consultation. The final ICER post-consultation was between £33,749 and £37,497 per QALY gained compared to SoC (excluding the confidential discount for blinatumomab received as subsequent therapy). The Appraisal Committee concluded that the ICER for inotuzumab was within the range usually considered cost-effective for end-of-life care, and recommended inotuzumab within its licensed indication.

**Key points for decision makers**

* Inotuzumab for the treatment of adult relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) is an effective bridge therapy, with improved rates of remission and progression to haematopoietic stem cell transplant treatment compared to standard of care.
* The company and other stakeholders were successful in appealing the initial negative recommendation on the grounds that the Appraisal Committee acted unfairly and that the recommendation was unreasonable in the light of the evidence; the company subsequently submitted a revised patient access scheme (PAS).
* Following new evidence on inpatient stay from clinical experts, updated subsequent therapy costs and with upward adjustments in the long-term utilities the deterministic ICER was between £33,749 and £37,497 per quality-adjusted life year (QALY) gained compared to standard of care.
* The NICE Appraisal Committee concluded that inotuzumab should be recommended within its licensed indication as a monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL.

# Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing evidence-based guidance to the National Health Service (NHS) in England for a range of health and social care issues. Single Technology Appraisals (STAs) evaluate a single technology with respect to a single indication. The STA process is designed to provide recommendations in the form of NICE guidance on the use of treatments in the NHS [1]. The company or sponsor of the technology submits the principal evidence supporting the clinical and cost-effectiveness of the product, and an external independent academic organisation, known as the Evidence Review Group (ERG), is commissioned to produce a review and critique of the evidence submitted [2]. Consultees, clinical specialists, NHS commissioning experts and patient representatives provide additional information for consideration by the NICE Appraisal Committee in formulating their guidance [1]. Once published, NICE technology guidance constitutes a legal obligation for NHS providers to reimburse an approved technology within its licensed indication [3].(2, 3)

NICE invited Pfizer, the manufacturer of inotuzumab ozogamicin (hereafter inotuzumab), to submit clinical and cost-effectiveness evidence for inotuzumab for the treatment of adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL), as part of the STA process. The Centre for Reviews and Dissemination and Centre for Health Economics at the University of York were commissioned as the independent Evidence Review Group (ERG). This article presents a summary of the ERG's independent report on the company's submissions to NICE, and the subsequent development of NICE guidance for the use of inotuzumab for the treatment of R/R B-cell ALL in adults. Full details of the relevant appraisal documents, including the appraisal scope, company and consultee submissions, ERG report, Appraisal Consultation Document (ACD), Final Appraisal Determination (FAD), company appeal and responses to these documents can be found on the NICE website [4].

# Decision Problem

Acute lymphoblastic leukaemia (ALL) is a type of cancer affecting the white blood cells. Whilst ALL is the most common type of childhood cancer, it is rarer in adults, and accounts for less than 1% of all new cancer cases in the UK [5]. The risk of mortality with ALL is highest in adults, who represent 40% of ALL cases, but constitute 80% of ALL deaths [6, 7]. Approximately three quarters of ALL patients have disease derived from precursor B-cells (B-cell ALL) while T-cell ALL comprises the remaining cases [8]. The majority of adult ALL patients under the age of 60 have Philadelphia chromosome negative (Ph-) disease which is associated with better outcomes compared with Philadelphia chromosome positive (Ph+) disease for those that relapse following initial treatment. Haematopoietic stem cell transplant (HSCT) is a potentially curative treatment option, although only available to patients who achieve a complete remission (CR) or complete remission with incomplete count recovery (CRi), and for whom a suitable donor can be found. Overall survival at 36-months is reported to be 11% in the overall Ph- population (including patients who did and did not receive prior HSCT), and greater than 20% in patients who received HSCT following first salvage therapy [9].

At the time of the appraisal there were no clinical guidelines from NICE relevant to the specific population of R/R B-cell ALL patients. Treatment options were limited and included chemotherapy-based regimens, tyrosine kinase inhibitors (TKI) alone or in combination with chemotherapy, or palliative care for those unfit for intensive treatment. The treatment landscape is evolving with the introduction of novel agents, and during the STA for inotuzumab, blinatumomab (Blincyto®) was recommended by NICE for treating adult patients with relapsed or refractory B-cell Ph- ALL [10].

Inotuzumab (Besponsa®) is a licensed anti-CD22 antibody drug conjugate indicated as monotherapy for the treatment of adults with R/R CD22-positive B-cell ALL where adult patients with Ph+ R/R B-cell ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI). The European Commission granted a marketing authorisation (in line with the draft marketing authorisation used in the appraisal) for inotuzumab in July 2017 [11].

NICE issued a final scope in December 2016 to appraise the clinical and cost-effectiveness of inotuzumab within its proposed license indication [12]. The scope specified three relevant comparators for Ph- and Ph+ patients able to tolerate chemotherapy: (i) fludarabine, cytarabine and granulocyte colony stimulating factor (FLAG)-based chemotherapy (Ph-), (ii) clofarabine-based combination chemotherapy (Ph-) and (iii) TKIs alone or in combination with FLAG- or clofarabine-based chemotherapy (Ph+). Blinatumomab was not included as a comparator in the final scope issued by NICE and was under appraisal at the time of the company’s submission to NICE (February 2017). Best supportive care (BSC) was the only specified comparator for patients unable to tolerate chemotherapy. The company submission omitted several comparators specified in the scope: clofarabine, TKIs alone and BSC. The company presented a comparison against chemotherapy “standard of care” (SoC) based on the investigator’s choice arm used in the INO-VATE 1022 trial [13], comprising one of the following three regimens: FLAG, cytarabine plus mitoxantrone (CM) or high-dose cytarabine (HIDAC).

# The Independent Evidence Review Group (ERG) Review

The company submitted evidence to NICE on the use of inotuzumab within its proposed licensed indication. The ERG critically evaluated the company’s evidence submission by assessing (i) whether the submission conformed to NICE methodological guidelines; (ii) whether the company’s interpretation and analysis of the evidence were appropriate; and (iii) the existence of other evidence and the impact of alternative interpretations of the evidence [2]. Additionally, the ERG identified areas requiring clarification, for which the company provided additional evidence and an updated cost-effectiveness model in accordance with STA procedures.

## Clinical Evidence

### Summary of the Clinical Evidence

The company described a systematic review of comparative studies of specified interventions used in the treatment of R/R B-cell ALL. The clinical effectiveness data presented by the company was primarily based on one international multicentre open label parallel group randomised controlled trial; the INO-VATE 1022 trial [13], which was designed to compare inotuzumab (n=164) to SoC (n=162), which was the investigator’s choice of FLAG (n=102), CM (n=38) or HIDAC (n=22). The trial exclusively recruited patients due to receive their first or second salvage therapy. The safety population comprised all randomised patients who received at least one dose of study drug (n=164 inotuzumab, n=143 SoC); the ITT218 population consisted of the first 218 patients recruited into the trial with at least 3 months follow-up post-randomisation; and the full intention to treat (ITT) population included all 326 randomised patients with the cut-off date set to the 248th survival event for all survival-related analyses (which was reached on 8 March 2016).

The trial met its primary objective by demonstrating that inotuzumab confers a statistically significant benefit in terms of achieving CR/CRi in the full ITT population (Table 1). A total of 73.2% inotuzumab patients achieved CR/CRi compared with 30.9% SoC patients; of which a significantly greater proportion with CR/CRi in the inotuzumab arm also achieved minimal residual disease (MRD) negativity (76.7%) compared with the SoC arm (38.0%). Inotuzumab was also associated with a statistically significantly higher proportion of patients progressing to HSCT after study therapy, and prior to the start of any post induction therapy than SoC; 43.3% versus 11.1%.

Based on the full ITT population, the median overall survival was 7.7 months (95% confidence interval (CI): 6.0 to 9.2) in the inotuzumab group and 6.7 months (95% CI: 4.9 to 8.3) in the SoC group. The INO-VATE 1022 trial did not meet its second primary objective of significantly longer overall survival in the inotuzumab group than the SoC group, at a prespecified two-sided boundary of P=0.0208. However, the overall survival data did not exhibit proportional hazards, with the separation of the curves in the Kaplan-Meier plots appearing after the median had been reached (at around 15 months). Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. The RMST estimates of overall survival at 37.7 months follow up were 13.9 months in the inotuzumab group and 9.9 months for SoC, with a difference of 3.9 months between groups (95% CI: 1.2 to 6.7).

Health-related quality of life (HRQoL) was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the 5-dimension European Quality of Life questionnaire (EQ-5D) and the EuroQol visual analogue scale (EQ-VAS). The results indicated improvement in scores for most dimensions of quality of life, functioning and symptoms on the EORTC QLQ-C30 scale for patients in the inotuzumab group, but the difference was only statistically significant in role functioning (64.7 inotuzumab versus 53.4 SoC), physical functioning (75.0 vs 68.1), social functioning (68.1 vs 59.8), and appetite loss (17.6 vs 26.3) . No statistically significant differences between groups in the EQ-5D or EQ-VAS scores were found (Table 1).

In the INO-VATE 1022 trial, 99.4% patients in the inotuzumab group and 100% patients in the SoC group reported treatment-emergent adverse events (TEAEs). Grade ≥3 TEAEs were reported by 90.9% patients in the inotuzumab group and 95.8% patients in the SoC group. Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. The most frequently reported TEAEs were thrombocytopenia (49.4% inotuzumab vs 60.8% SoC), neutropenia (48.8% vs 46.2%), anaemia (33.5% vs 55.2%), nausea (32.3% vs 47.6%) and pyrexia (31.7% vs 42.0%). However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm (22/164) than the SoC arm (1/143). Of the 22 cases of VOD in the inotuzumab treatment group, 5 cases were fatal. Table 1 displays a summary of the relevant clinical outcomes and event data submitted by the company.

[Table 1]

### Critique of the Clinical Evidence

The INO-VATE 1022 trial was considered to be of reasonable quality and broadly applicable to patients seen in NHS practice. However, the trial only included patients suitable for intensive therapy and due to receive their first or second salvage therapy, which represent a subset of the anticipated licensed population. It was unclear what previous chemotherapy regimens patients had relapsed on, and whether these previous regimens were relevant to UK practice.

The primary results of the trial, relating to CR/CRi, were considered reliable. Whilst remission outcomes were assessed by unblinded study personnel, the results for the full trial population were similar to those of the smaller ITT218 population, whose remission outcomes were assessed by an independent Endpoint Adjudication Committee. The results relating to the higher proportion of inotuzumab patients proceeding to HSCT were also likely to be reliable. However, some patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice. In addition, some patients did not receive HSCT, despite achieving CR/CRi.

The overall survival data presented by the company were subject to some limitations. RMST results were strongly dependent on the choice of truncation time. There was little difference between the treatment groups in the 18 month analysis requested by the ERG. The difference between groups only became statistically significant at 24 months, at which time few patients were included in the analysis (13 in the inotuzumab group and 5 in the SoC group). By 36 months only one patient was included in the analysis from each treatment arm. The RMST of 9.9 months for the SoC group was higher than other estimates presented by the company (range 3 to 5 months) [14-17] suggesting that the RMST analysis appears to overestimate overall survival.

The ERG had concerns that not all relevant comparators were included in the analysis. Clinical advice received by the ERG indicated that clofarabine-based chemotherapy regimens and TKIs alone (Ph+) are efficacious alternatives to current FLAG based regimes in UK clinical practice and ought to have been comparators. Given that blinatumomab was not used in the NHS at the time the NICE scope was finalised and was under appraisal itself during the STA process for inotuzumab, the ERG deemed it appropriate that blinatumomab was not included as a comparator.

There were concerns regarding the number of patients who completed HRQoL questionnaires after treatment and that the open label nature of the trial introduces potential bias for subjective endpoints. These limitations led the ERG to conclude that the company’s HRQoL findings should be interpreted with caution.

## Cost-Effectiveness Evidence

### Summary of the Cost-Effectiveness Evidence

The company's systematic review of published evidence on the cost-effectiveness, HRQoL, resource use and costs associated with inotuzumab and the treatment of R/R B cell ALL did not identify any relevant cost-effectiveness analyses. Consequently, the company developed its own model to assess the cost-effectiveness of inotuzumab. The model was in the form of a decision tree combined with a partitioned survival approach. The company assumed that patients surviving three years after receipt of HSCT would be cured and return to the mortality risk for the general population. The model split the patient population into three mutually exclusive sub-populations: (i) No CR/CRi and no HSCT; (ii) CR/CRi and no HSCT; (iii) HSCT and post-HSCT. Within each sub-population parametric survival models that included treatment as a covariate were used to extrapolate outcomes beyond the trial in terms of whether they were progression-free, post progression or dead. The model tracked the proportion of patients residing within each health state over time using 28-day time cycles. Tunnel states were incorporated within the HSCT and post-HSCT sub-population to capture the timing of HSCT.

The survival estimates for the first three years, treatment dosage and size of the sub-populations in the economic model was informed by analysis of the INO-VATE 1022 trial safety population, with the remaining inputs informed by studies identified in the cost-effectiveness review and other sources. Treatment was costed using the observed dosage and cycles administered in INO-VATE 1022, which for inotuzmab included patients who had up to 6 cycles of treatment (mean 2.83 cycles). The company included all patients within the safety dataset that had an HSCT, regardless of remission status, the timing of the transplant and whether this was received prior to any post-induction therapy. In each parametric survival model a treatment covariate was applied to the scale and shape parameters, with the estimated additional treatment-specific survival benefits extrapolated up to the cure point.

The company applied a discount rate of 1.5% per annum to both costs and outcomes based on an assumption that HSCT can restore patients to ‘normal’ life expectancy. Costs were considered from an NHS and Personal Social Services perspective and were based on prices from 2015 to 2016. The economic model included costs associated with treatment, HSCT procedures, adverse events, inpatient and outpatient stays from treatment administration, and end of life care. A lifetime horizon was used to estimate costs and benefits and a half cycle correction was applied.

The deterministic base case incremental cost-effectiveness ratio (ICER) for inotuzumab compared to SoC was £40,013 per quality-adjusted life-year (QALY). Inotuzumab was estimated to provide an additional 5.2 life years and 2.2 quality-adjusted life years (QALYs), with the majority of the QALY gain conferred within the HSCT and post-HSCT sub-population. Using a discount rate of 3.5% on costs and health outcomes, the deterministic base case ICER was £55,869/QALY.. The company reported that the most influential parameters in one way sensitivity analyses were the cost of HSCT, the cost and usage of blinatumomab subsequent to SoC, the HRQoL values associated with progressed disease, and the HRQoL values assigned more than five years after HSCT.

### Critique of the Cost-Effectiveness Evidence

The ERG’s critical appraisal of the company’s cost-effectiveness evidence identified a number of issues. The ERG felt that splitting the INO-VATE 1022 trial into three post-hoc sub-populations and fitting multiple parametric survival models that incorporated treatment effects on both the shape and the scale of the hazard was overly complex. The parametric models fit to the HSCT and post-HSCT sub-population constituted a non-randomised comparison and did not provide a suitable basis for extrapolation. The imposition of a cure point at three years was required to prevent clinically implausible estimates for SoC. The shapes of the hazard functions suggested that HSCT can only be potentially curative (i.e. the hazard declines over time to 0) for patients who have been treated with inotuzumab but not SoC. This relationship and the associated predicted survival estimates was in conflict with the existing epidemiological evidence which showed hazards decreasing with time and overall survival rates higher than those predicted for SoC [13]. The ERG was concerned with the lack of robust evidence supporting the additional survival benefit from inotuzumab incorporated into the model after receipt of HSCT. The company included an exploratory analysis in which post-HSCT survival was informed by MRD status with treatment specific rates of MRD negativity among patients achieving remission in INO-VATE 1022. The ERG thought that, while highly uncertain, this was potentially more clinically plausible and with better external validity compared to the company base case.

The ERG noted that there was no structural link in the company model between remission outcomes and HSCT. The lack of a structural link did not reflect the role of inotuzumab as a bridge therapy and prevented subgroup analysis around patient characteristics that can influence the rate of HSCT.

The company had made a significant effort to source relevant estimates of HRQoL. The ERG considered that the utility values derived from INO-VATE 1022 and those taken from the literature constituted the best available evidence. HRQoL values were particularly low in cases of progression (0.3) or VOD (0.208). There was however some inconsistency between the cure assumption and the epidemiological data on long term survival post-HSCT which indicates that progression-free patients continue to experience higher morbidity for a sustained period relative to the general population [18]. The ERG considered utilities from INO-VATE 1022 should be pooled and that utilities in the HSCT and post-HSCT state (0.74) should be adjusted for age in line with NICE methods guidance [3].

The ERG identified several areas of uncertainty in the costs due to differences between the treatments provided to the SoC group in INO-VATE 1022 and current NHS practice. The company applied the costs of idarubicin to SoC and TKI costs for Ph+ patients despite these not being provided in INO-VATE 1022. The rates of blinatumomab and post-induction inotuzumab were based on the ITT population. The ERG preferred consistency between the efficacy outcomes and cost assumptions, and felt that the inclusion of INO-VATE 1022 subsequent therapy costs was potentially inappropriate, because it was unclear whether the benefits from post-induction therapies were adequately reflected in the safety population that formed the basis for the survival analysis. The length of stay and patient setting required for the administration of inotuzumab (3 outpatient visits per cycle) and standard chemotherapy (approximately 5.23 inpatient days) assumed in the company model appeared misaligned with standard practice. Clinical advice received by the ERG indicated that standard chemotherapy and the first cycle of inotuzumab are likely to be administered in an inpatient setting, with patients remaining hospitalised for significantly longer than the recommended administration schedules used by the company due to the recovery period. Following clarification by the company, data wereacquired from INO-VATE 1022 which reported a significant proportion of patients had received inotuzumab in an inpatient setting. Furthermore, recent case studies identified by the ERG reported mean length of hospitalisation for Ph-negative R/R ALL patients between 16.8 days (France) and 26 days (Spain) [19, 20].

The ERG considered that the criteria for applying a discount rate of 1.5% to costs and outcomes were not met [3]. Epidemiological data and the results of INO-VATE 1022 indicate ongoing morbidity following receipt of HSCT, and evidence suggests that mortality rates remain four to nine-fold higher compared to the general population for upward of 25 years [21].

Due to the aforementioned concerns, the ERG did not consider the company’s cost-effectiveness evidence for inotuzumab versus SoC sufficiently reliable to inform decision making. The results of ERG preferred scenario analyses are shown in Table 2. The combination of the scenarios resulted in an ICER for inotuzumab compared to SoC of £114,078 per QALY gained with parametric survival models fit to the trial data and £122,174 per QALY gained using Kaplan Meier survival estimates. ICERs calculated in the additional scenario analyses surrounding the ERG’s non-parametric base case ranged between £121,648/QALY (all SoC costed as FLAG-IDA) and £84,065/QALY (separate survival curves post-HSCT).

[Table 2]

## Conclusions of the ERG Review

INO-VATE 1022 demonstrated that inotuzumab had a significant benefit in terms of improving remission outcomes and was associated with a statistically significantly higher proportion of patients progressing to HSCT after study therapy than SoC. However, the data on overall survival were less convincing. Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, VOD, a potentially fatal event, was statistically significantly more frequent in the inotuzumab arm than the SoC arm. The INO-VATE 1022 trial only included patients who were suitable for intensive therapy and due to receive their first or second salvage therapy, which is only a subset of the anticipated licensed population.

The key drivers in the cost-effectiveness evaluation of inotuzumab were the assumptions concerning the additional benefits of inotuzumab post-HSCT. The ERG considered that the criteria for applying a 1.5% discount rate were not met, and that the assumption that patients would return to general population morbidity and mortality risk three years post-HSCT was not supported by epidemiological evidence. Given these concerns and others (see Table 2), the ERG did not consider the company’s estimates of cost-effectiveness to be reliable. The ICER for inotuzumab versus SoC when using the ERG’s preferred assumptions was between £114,078 per QALY gained and £122,174 per QALY gained.

# NICE Appraisal Committee: Consideration of All Available Evidence

## Preliminary Guidance Prior to Appeal

On balance of the evidence submitted by the company and the views of consultees, commentators, clinical experts and patient experts, the NICE Appraisal Committee concluded that inotuzumab is clinically effective, met NICE’s criteria to be considered as an end of life treatment, and believed that the ERG’s parametric base case most closely reflected the Committee’s preferred assumptions. It was adjudged that the availability of inotuzumab would be beneficial for patients, but that the ICER for inotuzumab was too high to be considered as a cost-effective use of NHS resources for a life-extending end of life treatment (>£100,000/QALY) [22].

### Company’s Response to the Appraisal Consultation Document (ACD)

Following the first Appraisal Committee meeting, the company submitted a patient access scheme (PAS) and in response to the ACD undertook new cost-effectiveness analyses, provided new data on subsequent therapies prescribed in the safety population of INO-VATE 1022 and reported a revised base case which incorporated the new PAS.

The company accepted and incorporated a number of changes into their revised base case in accordance with the committee’s preferences. Changes included using a 3.5% discount rate for costs and QALYs, age adjusted utilities, chemotherapy costs in line with treatments provided in INO-VATE 1022 and pooled on-treatment utilities. However, five of the assumptions underpinning the Committee’s preferred base case were rejected. Table 3 outlines the following five changes which were applied to the Committee’s preferred base case in conjunction with the PAS to obtain the company’s revised base case. The resulting company base case had an ICER of £37,734 per QALY gained for inotuzumab compared to SoC.

[Table 3]

The company structured their response around three areas: a comparison against the NICE final guidance for blinatumomab, the alternative assumptions underpinning the company’s preferred ICER (Table 3) and an additional scenario regarding the number of cycles of inotuzumab [23]. The company stated that there are a number of key modelling assumptions applicable to inotuzumab which NICE accepted when recommending blinatumomab (i.e. treatment specific parametric curves and general population utilities and mortality risk beyond the post-cure point). The updated company analysis reverted to treatment specific Kaplan Meier curves and the original subsequent therapy costs, and applied alternative post-cure mortality risks, post-cure utilities and administration schedules for inotuzumab and SoC. Furthermore, the company claimed that all patients who "achieved CR/CRi and MRD negativity" with inotuzumab did so within the first three cycles and that an alternative scenario applying a maximum of 3 cycles for patients proceeding to HSCT is a “*highly relevant*” scenario for decision making.

### ERG Critique of the Company’s Response to the ACD Consultation

The ERG argued that the company’s comparison against NICE final guidance for blinatumomab was not relevant. The company had chosen not to make a comparison against blinatumomab in their original model. The drugs are different products with a different mechanism of action, different methods of administration, different prices and a different underlying evidence base, all of which may reasonably lead to differences between the appraisals. The ERG believed that including the cost of subsequent therapies was appropriate in light of the new evidence provided on the rates of use in the safety population (Table 3). The company had presented no new information with respect to the use of treatment specific parametric survival curves, HRQoL or administration costs, whilst the choice of references and analyses surrounding the revised mortality risk were fundamentally flawed [23]. Moreover, the ERG also had concerns as to whether all patients who achieved CR/CRi and/or received HSCT had no more than 3 cycles of inotuzumab and concluded that costing only three cycles of inotuzumab cannot be regarded as consistent with the efficacy in the model.

Applying the company’s preferred cost of subsequent therapies and the PAS to the committee’s original preferred base case generated a deterministic ICER which remained greater than £50,000 per QALY gained.

### The Appraisal Committee’s Initial Guidance

In August 2017 the NICE Appraisal Committee recalled its preferred assumptions and emphasised that the cost-effectiveness estimate for inotuzumab compared with current treatment (FLAG-based chemotherapy) remained substantially higher than what NICE considers acceptable for end-of-life treatments [24]. The committee accepted that the cost of subsequent therapy should be based on the safety population, and that there would be a difference in the number of inpatient days for patients having inotuzumab and SoC.

## Preliminary Guidance Post-Appeal

### Company appeal

Following the NICE Appraisal Committee’s decision not to recommend inotuzumab, the company and other stakeholders lodged separate appeals on the grounds that NICE had failed to act fairly and that the recommendation was unreasonable in light of the evidence submitted to NICE [25]. A NICE panel upheld the appeal on the basis that: (i) the committee provided no explanation for rejecting the utilities proposed by the company post-consultation; (ii) the reasons given for disregarding key assumptions used in the blinatumomab appraisal do not explain the choices made in relation to inotuzumab; and (iii) that it was not reasonable to fail to consider properly and rigorously a model of treatment (a maximum of 3 cycles) which is standard UK practice [26]. The appeal panel dismissed three other grounds for appeal made by the company. In February 2018, NICE requested the company use an analysis that matched the committee preferred assumptions as a starting point for additional appeal-based analyses and for the company to provide an update regarding inotuzumab’s post-appeal PAS status. The company’s response provided an interpretation of the committee’s favoured analysis, detailed company preferred adjustments in relation to upheld appeal points and reported a revised PAS with a larger discount [27]. The company’s post-appeal analysis, including the revised PAS, resulted in a deterministic ICER of £33,649.

In the third Appraisal Committee meeting the committee considered each upheld appeal point. The committee accepted that utility values 5 years post-HSCT may lie between those found in the literature [18] and the general population (0.76-0.88) and that the trial mean 2.83 cycles costed in the original model was appropriate as it best aligned the number of cycles with the efficacy data. It was considered that no further changes to the base case were necessary to respond to specific appeal points. The committee reconsidered the available evidence and concluded that the number of inpatient days for inotuzumab and SoC should be updated using the available “*robust clinical data*” outlined by clinical experts at the meeting. The committee was minded not to recommend inotuzumab, but delayed making a final recommendation, concluding that further analyses were required to reflect the committee’s preferred assumptions on utility post-HSCT and new clinical data on the number of inpatient days [28].

In June 2018, the NICE Appraisal Committee reconvened and used a revised cost-effectiveness analysis with the committee’s preferred assumptions to inform decision making. The updated analysis applied the following changes to the committee‘s original base case prior to the appeal: utility values for all patients 5 years post-HSCT set between 0.76 and 0.88; using the generic price for imatinib and the price of blinatumomab with its PAS in place; alternative inpatient stays using observational data from the inotuzumab compassionate use programme; and the revised PAS discount. Withholding blinatumomab’s PAS, the committee’s preferred assumptions resulted in a deterministic ICER of £37,497/QALY when using utility values taken from the literature (0.76) and £33,749/QALY when using utility values from the general population (0.88).

## The Appraisal Committee’s Final Guidance

In August 2018, the NICE Appraisal Committee published the following final guidance to the NHS:

“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” [29].

Complete details of the guidance, the Appraisal Committee’s consideration of the evidence, each company response to NICE and the appeal process is available on the NICE website [4].

# Conclusions

This STA highlights some of the difficulties in appraising bridging therapies, where health gain is principally achieved by a small subset of patients (those eligible for curative therapy). The value of the bridge therapy is primarily determined by the HSCT decision making process and the benefits offered by the procedure. Long term survival data from HSCT, a technology that has significantly altered in the past few decades, is highly uncertain even with the most up to date existing epidemiological evidence and expert clinical advice.

This appraisal also highlights the role that the appeal process can have in formulating guidance. In this case, preliminary guidance was overturned by post-appeal proceedings with committee preferred assumptions updated in light of new forms of evidence and additional expert clinical advice and the company having submitted an improved PAS. It should also be noted that this appraisal marked the issues faced when multiple appraisals for the same indication run in tandem. Blinatumomab, which is a licensed treatment for adults with Ph- R/R B-cell ALL, was recommended by NICE during the appraisal for inotuzumab. Since blinatumomab was not a recommended therapy at the beginning of the appraisal process it was not included as a comparator, meaning conclusions about the cost-effectiveness of inotuzumab versus blinatumomab cannot be made for this population. Instead the company used NICE final guidance for blinatumomab as a means of justifying preferred assumptions in relation to inotuzumab, despite the appraisals using different modelling approaches and having different underlying evidence bases (e.g. overall survival was significantly longer in the blinatumomab group than SoC). Despite considerable discussion, committee preferred assumptions were not altered as a result of the comparison between appraisals.

Overall, the ERG was able to identify a variety of important limitations in the data and the economic model; this led the NICE Appraisal Committee’s preferred assumptions and initial estimates of cost-effectiveness to differ widely from those reported by the company. This reinforces the importance of recommendations being informed by an independent critique of the evidence.

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**Author Contributions**

Edward Cox, Ros Wade, Mathilde Peron, Kristina Charlotte Dietz, Alison Eastwood, Stephen Palmer and Susan Griffin were all members of the ERG that produced the ERG report described in this paper. Steven Palmer and Alisson Eastwood took overall responsibility for the cost and clinical effectiveness parts of the project. Edward Cox wrote the draft of the manuscript. All authors commented on the manuscript and approved the final version. This summary has not been externally reviewed by PharmacoEconomics.

**Compliance with Ethical Standards**

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**Conflict of Interest**

Edward Cox, Ros Wade, Mathilde Peron, Kristina Charlotte Dietz, Alison Eastwood, Stephen Palmer and Susan Griffin declare that they have no conflict of interest.

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# Tables

**Table 1** Summary of the clinical evidence

|  |  |
| --- | --- |
|  | ITT population (N=326) |
| Inotuzumab (N=164) | SoC (N=162) |
| CR/CRi, n (%) | 120 (73.2) | 50 (30.9) |
| CR/CRi & MRD negative, n (%) | 92/120 (76.7) | 19/50 (38.0) |
| HSCT, n (%)  | 71 (43.3) | 18 (11.1) |
| EQ-5D Index, (95% CI) | 0.80 (0.77, 0.82) | 0.76 (0.73,0.80) |
| EQ-VAS, (95% CI) | 67.1 (64.0, 70.2) | 62.5 (57.6, 67.4) |
|  | Safety population (N=307) |
|  | Inotuzumab (N=164) | SoC (N=143) |
| AEs, n (%) | 163 (99.4) | 143 (100) |
| SAEs, n (%) | 84 (51.2) | 71 (49.7) |
| Grade ≥3 TEAE | 149 (90.9) | 137 (95.8) |
| TEAE, n (%) |  |  |
| Thrombocytopenia | 81 (49.4) | 87 (60.8) |
| Neutropenia | 80 (48.8) | 66 (46.2) |
| Anaemia | 55 (33.5) | 79 (55.2) |
| Nausea | 53 (32.3) | 68 (47.6) |
| Pyrexia | 52 (31.7) | 60 (42.0) |
| VOD | 22 (13.4) | 1 (0.7) |

ITT: Intention to treat; EQ-5D: EuroQol five dimensions; EQ-VAS: EuroQol Visual Analogue Scale; SoC: Standard of care; CI: Confidence interval; CR: Complete remission; CRi: Complete remission without count recovery; MRD: Minimal residual disease; HSCT: Haematopoietic stem cell transplant; AE: Adverse event; SAE: Serious adverse event; TEAE: Treatment emergent adverse event; VOD: Veno-occlusive disease

**Table 2** Overview of the ERG preferred scenario analyses

|  |  |
| --- | --- |
| ERG scenario analyses and base cases  | ICER, £/QALY gained |
|  | 1.5% discount rate | 3.5% discount rate |
| Company base case | £40,013 | £55,869 |
| Minor costing correctiona | £39,949 | £55,779 |
| Age adjusted utilities | £43,909 | £60,260 |
| Chemotherapy costs in line with INO-VATEb | £41,021 | £57,287 |
| Pooled on treatment utilities | £40,076 | £55,992 |
| Subsequent therapy costs equal to chemotherapyc | £44,082 | £61,594 |
| NHS administration costs using INO-VATE patient settingd | £41,389 | £57,804 |
| Fourfold increase in risk of mortality post-cure | £53,069 | £68,381 |
| Non-parametric - pooled survival curves post-HSCT  | £61,021 | £83,060 |
| Parametric - pooled survival curves with MRD adjustment post-HSCTe | £56,819 | £77,783 |
| ERG non-parametric base casef | - | £122,174 |
| ERG parametric base caseg | - | £114,078 |

ERG Evidence Review Group; ICER Incremental cost-effectiveness ratio; QALY quality-adjusted life-year; MRD: Minimal residual disease

a Proportion of patients receiving treatments CM and HIDAC in cycle 2 linked to CM/HIDAC as opposed to FLAG

b Removing the costs of TKI imatinib for Ph+ and splitting SoC patients between FLAG, CM and HIDAC excluding the costs of idarubicin

c The cost for a patient receiving blinatumomab and inotuzumab are replaced with the cost of standard of care chemotherapy

d Alternate administration costs are based on a weighted average NHS reference cost. The patient setting for inotuzumab administration is aligned with INO-VATE 1022 which includes a proportion of administration delivered in an inpatient setting.

e Pooled survival data post-HSCT with a covariate adjustment for MRD negativity, combined with treatment specific rates of MRD negativity among patients achieving remission in INO-VATE 1022

f The combination of the ERG preferred scenarios with the exception of the parametric – pooled survival curve with MRD scenario

g The combination of the ERG preferred scenarios with the exception of the non-parametric - pooled survival curves post-HSCT scenario

**Table 3** Overview of the rejected committee preferred assumptions in the company’s revised base case (submitted in response to the ACD prior to appeal)

SoC: Standard of care; MRD: Minimal residual disease; HSCT: Haematopoietic stem cell transplant; FLAG: Fludarabine, cytarabine and granulocyte colony stimulating factor; NICE: National Institute for Health and Care Excellence

|  |  |  |
| --- | --- | --- |
| **Rejected committee preferred assumptions** | **Alternative assumptions used in company’s revised base case** | **Company justification** |
| Parametric pooled survival curves with a covariate adjustment for MRD negativity | Reverting back to the company’s original parametric curves fit to Kaplan-Meier data for survival post-HSCT | To model the survival probabilities of patients post-HSCT, treatment specific Kaplan-Meier data from patients post-HSCT is the best available data source |
| Fourfold increase in risk of mortality post-cure | Mortality risk 3.0x general population for MRD+ and 1.6x for MRD- patients. This equates to mortality risk of 2.5x general pop for SoC, and 1.9x for inotuzumab | A historical cohort can be misrepresentative of the outcomes expected for patients treated today |
| NHS administration costs using INO-VATE 1022 patient setting  | •The first administration of inotuzumab within the first cycle costed in an inpatient setting•FLAG costed with a 14-day inpatient stay | The clinical expert at the committee meeting stated that “several weeks” of inpatient stay is common for FLAG-based chemotherapy |
| Subsequent therapy costs equal to chemotherapy costs  | Reverting back to subsequent therapies costed from the safety population observed in INO-VATE 1022  | The (new) data shows all subsequent blinatumomab and inotuzumab was administered to the safety population, proving that using the safety population does not introduce treatment bias |
| Utility values post-cure taken from the literature [18] | General population utilities applied instead of those sourced from the literature | The NICE committee for blinatumomab accepted that patients who pass the cure point post-HSCT can expect a return to the health-related quality of life (utility) of the normal population |