NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Contains AIC ,CIC

Pre-meeting briefing

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Common abbreviations

Abbreviation	Definition
ALL	Acute lymphoblastic leukaemia
CM	Cytarabine plus mitoxantrone
CR	Complete response
CRi	Complete response with incomplete count recovery
FLAG	Fludarabine, cytarabine and granulocyte-colony stimulating factor
GvHD	Graft versus host disease
HIDAC	High dose cytarabine
HRQL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
MRD	Minimal residual disease
Ph+/-	Philadelphia-chromosome positive/negative
RMST	Restricted mean survival time
R/R	Relapsed and refractory
VOD	Veno-occlusive liver disease

Disease background

- Acute lymphoblastic leukaemia (ALL) is a rapidly progressing form of cancer of the white blood cells
- Rare - 0.2% of new cancers in UK
- Predominately disease of childhood but affects adults too
- 42% of cases in adults
- Symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- 75% of ALL is derived from precursor B-cells (B-cell ALL)[a]
- Most B-cell ALL is Philadelphia chromosome negative (Ph-); Ph-positive (Ph+) disease is associated with worse outcomes
- Approximately 44% of adult B-cell ALL patients are expected to relapse and 4% are refractory to available treatments[b]
- 5-year overall survival <10%[c]
- Estimated ALL R/R B-cell population in England is 117 patients[d]

Key: a, b, c, d, company submission.
Note: The estimate of 117 pts is based on estimated 82% of ALL being B-cell, not 75%.

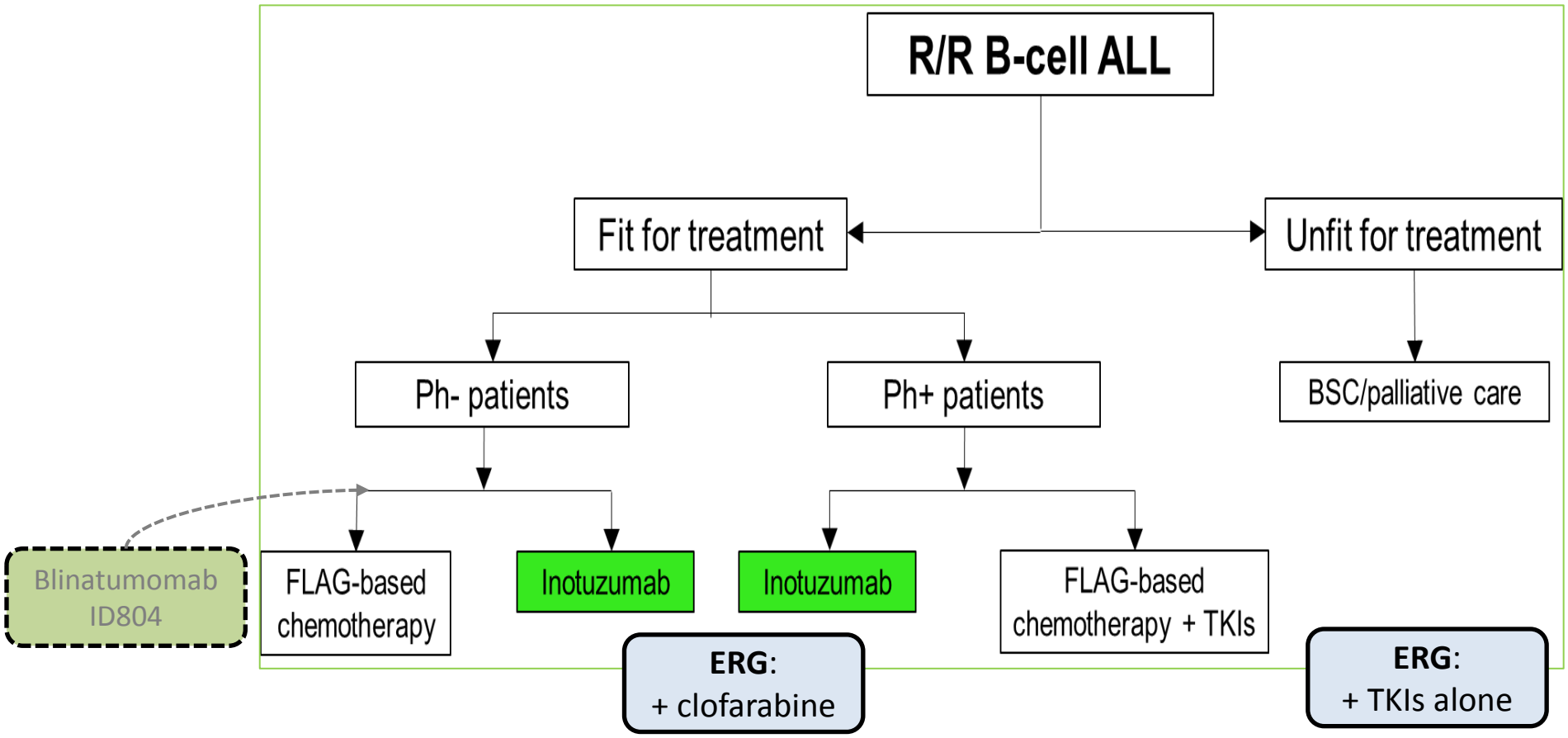
Disease management

- Limited treatment options
- Relapsed and refractory (R/R) ALL is treated by combination chemotherapy with poor response and considerable toxicity
- The aim of chemotherapy is complete remission (CR) or CR with incomplete haematological recovery (CRi), so patients can have haematopoietic stem cell transplant (HSCT) that can potentially cure the patient
- Current treatment
  - Fludarabine, cytarabine and granulocyte-colony stimulating factor (GCSF) based combination chemotherapy (FLAG), and FLAG with idarubicin (FLAG-IDA),
  - clofarabine-based regimens (CDF group 3) for R/R ALL (sometimes used off label)
  - Tyrosine kinase inhibitors (TKIs) alone or in combination with FLAG- or clofarabine-based chemotherapy for Philadelphia-chromosome-positive (Ph+) ALL

Inotuzumab ozogamicin (Besponsa, Pfizer)

Marketing authorisation	Besponsa 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 (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor.
Mechanism of action	Inotuzumab ozogamicin is an antibody-drug conjugate of a monoclonal antibody. When inotuzumab ozogamicin binds to a CD22 antigen on a B-cell, it is absorbed into a malignant cell and leads to cell death.
Administration	Intravenous infusion
Acquisition cost	Solution for infusion: [redacted] per 1-mg vial (price not DH approved)
Cost of a course of treatment	Over the course of treatment, it is estimated that an average of [redacted] vials will be administered: [redacted]

Treatment pathway



Key: ALL, acute lymphoblastic leukaemia; BSC, best supportive care; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; Ph-, Philadelphia chromosome negative; Ph+ Philadelphia chromosome positive; R/R, relapsed or refractory; TKIs, tyrosine kinase inhibitors.

Patients and carers comments

- Most patients with relapsed or refractory ALL will be extremely ill, having undergone (and not responded well to) highly toxic treatment
- The majority of patients treated with highly toxic salvage chemotherapy would spend around half of their time in hospital
- Many patients (particularly older or less fit adults) are unable to tolerate these aggressive options and receive best supportive care. As such, there is an urgent need for these patients in this setting to access further treatment options
- The vast majority of patients (over 90%) will die from their disease within a short period of time, usually within a few months because there are such limited options for relapsed or refractory patients

Clinical expert comments (2x)

- *The current salvage chemotherapy has a low chance of success and is extremely toxic almost always causing bacterial and sometimes fungal infections.*
- *There are no relevant clinical guidelines for relapsed ALL and no standard of care.*
- *…show benefit in remission rate and in survival; importantly, the benefit applies even in some of the worst prognostic groups….*
- *Relative lack of side effects compared to combination chemotherapy…*
- *A particular adverse effect of potential concern is veno-occlusive disease*
- *can be given in an outpatient setting*
- *The Inovate study … is not entirely applicable to a UK setting*
- *The overall goal of treatment of relapsed ALL in adults is long term diseasefree survival equating to 'cure'...the steps…are:*
  1. *To achieve complete remission (CR)…There are other definitions of response such as CRi … the predictive meaning of which is not clear... the predictive value of MRD in relapse OR after using nonchemo agents is NOT YET ESTABLISHED.*
  2. *To achieve an allogeneic bone marrow transplant wherever possible.*

Leukaemia CARE comments

- *Being diagnosed with ALL can also have a huge emotional impact… in our survey, 60% of ALL patients reported that they have felt depressed or anxious more often since their diagnosis.*
- *ALL is often diagnosed as an emergency (64%), with 86% of patients starting treatment within a week of diagnosis.*
- *has a significant symptom burden (fatigue, breathlessness, sleeping problems, nausea, vomiting, memory loss, pain), as well as a financial and emotional impact.*
- *Treatment options are limited, most likely to salvage chemotherapy. Only a small proportion of patients would currently be eligible for allo-SCT, the only curative option, offering the most effective and durable disease control.*
- *Inotuzumab ozogamicin offers a number of potential benefits, including improved response rates and longer survival (PFS and mean OS).*
- *Another key benefit of inotuzumab ozogamicin is its potential as a bridge to transplant, the only curative option for these patients. This was welcomed by 91% of ALL patients in our recent survey.*

Decision problem (I)

	Final NICE scope	Company submission	ERG comments
Population	Adults with relapsed or refractory B-cell acute lymphoblastic leukaemia		Only a subset included: adults fit for intensive therapy, chemotherapy and transplantation. Patients who would be treated with BSC and patients who were due to receive salvage therapies beyond Salvage 2 not included in INO-VATE 1022. The MA and scope population is broader.
Intervention	Inotuzumab ozogamicin		INO-VATE 1022: inotuzumab at the recommended dose, for up to 6 cycles (median 3.0 cycles).

Decision problem (II)

	Final NICE scope	Company submission	Rationale	ERG comments
Comparators	<u>Fit for chemotherapy</u> • *Ph- ALL*: − FLAG-based chemotherapy − clofarabine-based chemotherapy (CDF) • *Ph+ ALL*: − TKIs alone or in combination with FLAG- or clofarabine-based chemotherapy <u>Unfit for chemotherapy:</u> − BSC	<u>Fit for chemotherapy</u> Based on INO-VATE 1022 investigator's choice arm (FLAG, CM & HIDAC based chemotherapy) • *Ph- ALL:* − FLAG-based chemotherapy • *Ph+ ALL*: − TKIs in combination with FLAG-based chemotherapy	• Clofarabine: off label use in <5% of the population • TKIs alone: unlikely to be used alone • BSC: not relevant comparator inotuzumab acts as a bridge to HSCT	• Clofarabine: used in UK clinical practice should be included • TKIs alone: important for Ph+ ALL should be included • BSC: not appropriate comparator • CM & HIDAC not in NICE scope not used in current practice.

Decision problem (III)

	Final NICE scope	Company submission	ERG comments
Outcomes	• Overall survival • Progression-free survival • Treatment response rates (including haematologic responses) • Time to and duration of response • Adverse effects of treatment • HRQL	As per scope plus: • Minimal residual disease negativity (MRD-) • Rate of potentially curative therapy, such as HSCT	Appropriate, however the predictive value of MRD in relapse OR after using non-chemo agents is not yet established.
Economic analysis	Costs will be considered from an NHS and Personal Social Services perspective.	Base case: Costs and QALYs discounted at an annual rate of 1.5% based on assumptions that HSCT can potentially restore patients to normal life expectancy	The assumptions post HSCT not consistent with criteria for 1.5 % discount rate. Receipt of HSCT does not restore normal life expectancy in near full health.

Preview: Clinical effectiveness and treatment pathway issues

1. How would inotuzumab fit into the current treatment pathway?
   - What are the appropriate comparators? Are clofarabine and TKIs alone relevant comparators for some people?
   - Can inotuzumab be used in outpatient setting?
2. Is the “fit for treatment” population in INO-VATE 1022 reflective of NHS practice?
3. What is the prognosis for relapsed or refractory ALL?
4. The INO-VATE 1022 trial compared inotuzumab with investigator’s choice (SoC). Is SoC reflective of NHS practice?
5. How generalisable are INO-VATE 1022 results?
   - What is the most relevant population, ITT, ITT218, safety population?
   - Are RMST OS analyses appropriate?
   - Not all CR/CRi patients in INO-VATE 1022 had HSCT and some had HSCT without CR/CRi

Preview: Cost-effectiveness issues

1. Is 1.5% cost and QALY's discount rate appropriate for decision making?
2. OS data
   - Is the OS modelling in the *HSCT & Post-HSCT* state appropriate
   - Is the assumption of the "cure point" at 3 years appropriate?
   - What is the mortality rate after HSCT?
3. Cost
   - How should be the administration cost of inotuzumab modelled?
   - Is it appropriate to add the cost of idarubicin and imatinib to the cost of SoC?
   - Should the cost of subsequent therapies be included in the model?
4. Were appropriate utilities used in the model?
5. Are the end-of-life criteria met?
6. What is the most plausible ICER?

Clinical effectiveness evidence

Trial evidence: INO-VATE1022

Design	• Open-label, multicentre phase 3 open-label RCT
Location (sites)	193 sites in 25 countries 8 sites in the UK = 5.2% of enrolled patients; 4 in inotuzumab ozogamicin (inotuzumab) and 5 in in standard of care (SoC)
Population	• Adults (18yrs +) with R/R CD22-positive ALL (ECOG 0-2) due to receive either Salvage 1 or Salvage 2 therapy • Patients with Ph+ ALL failed treatment with at least 1 second- or third-generation TKI.
Intervention and comparator	ITT=326: Inotuzumab (n=164) and SoC (n=162) • FLAG based regimen: (63%; 102/162) • Cytarabine plus mitoxantrone: (23%; 38/162) • HIDAC based regimen: (14%; 22/162)
Primary outcome measures	CR (including CRi) and OS: last follow-up at March 2016 (data cut-off of 37.7 months). [redacted] recommended 1-sided test (0.025) for OS
Secondary outcome measures	PFS, minimum residual disease (MRD), duration of remission (CR and CRi), rate of subsequent HSCT, EORTC QLQ-C30, EQ-5D, safety

INO-VATE1022: baseline

	ITT218 population[a]		ITT population	
	Inotuzumab (N = 109)	SoC (N = 109)	Inotuzumab (N = 164)	SoC (N = 162)
Age, median (range)	47 (18.78)	47 (18–79)	46.5 (18–78)	47.5 (18–79)
Male, n (%)	61 (56)	73 (67)	91 (55.5)	102 (63.0)
Race[b], white, n (%)	76 (70)	79 (72)	112 (68.3)	120 (74.1)
ECOG PS, n (%)[c]				
• 0	43 (39)	45 (41)	62 (37.8)	61 (37.7)
• 1	50 (46)	53 (49)	81 (49.4)	80 (49.4)
• 2	15 (14)	10 (9)	21 (12.8)	20 (12.3)
• Missing data	1 (1)	1 (1)	0	1 (0.6)
Salvage-treatment phase, n (%)				
• First	73 (67)	69 (63)	111 (67.7)	104 (64.2)
• Second	35 (32)	39 (36)	51 (31.1)	57 (35.2)
• Missing data	1 (1)	1 (1)	2 (1.2)[d]	1 (0.6)[d]
Previous HSCT, n (%)	17 (16)	22 (20)	29 (17)	31 (18)

Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HSCT, haematopoietic stem cell transplantation; NR, not reported; Ph, Philadelphia chromosome; SoC, standard-of-care

INO-VATE1022: remission outcomes (I)

ITT population	Inotuzumab N=164	SoC N=162	Rate difference	P-value
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	[redacted]
CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	[redacted]
CR/CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	[redacted]
MRD negativity in CR/CRi patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
MRD positive in CR/CRi patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
No MRD results in CR/CRi patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; MRD, minimal residual disease SoC, standard of care.

INO-VATE1022: remission outcomes (II)

ITT228 population	Inotuzumab N=109	SoC N=109	Rate difference	p-value
CR/CRi, n (%)	88 (80.7)	32 (29.4)	51.4	<0.0001
95% CI for rate; 97.5% CI for rate difference	72.1, 87.7	21.0, 38.8	38.4, 64.3	
CR, n (%)	39 (35.8)	19 (17.4)	18.3	0.002
95% CI for rate; 97.5% CI for rate difference	26.8, 45.5	10.8, 25.9	5.2. 31.5	
CRi, n (%)	49 (45.0)	13 (11.9)	33.0	<0.0001
95% CI for rate; 97.5% CI for rate difference	35.4, 54.8	6.5, 19.5	20.3, 45.8	

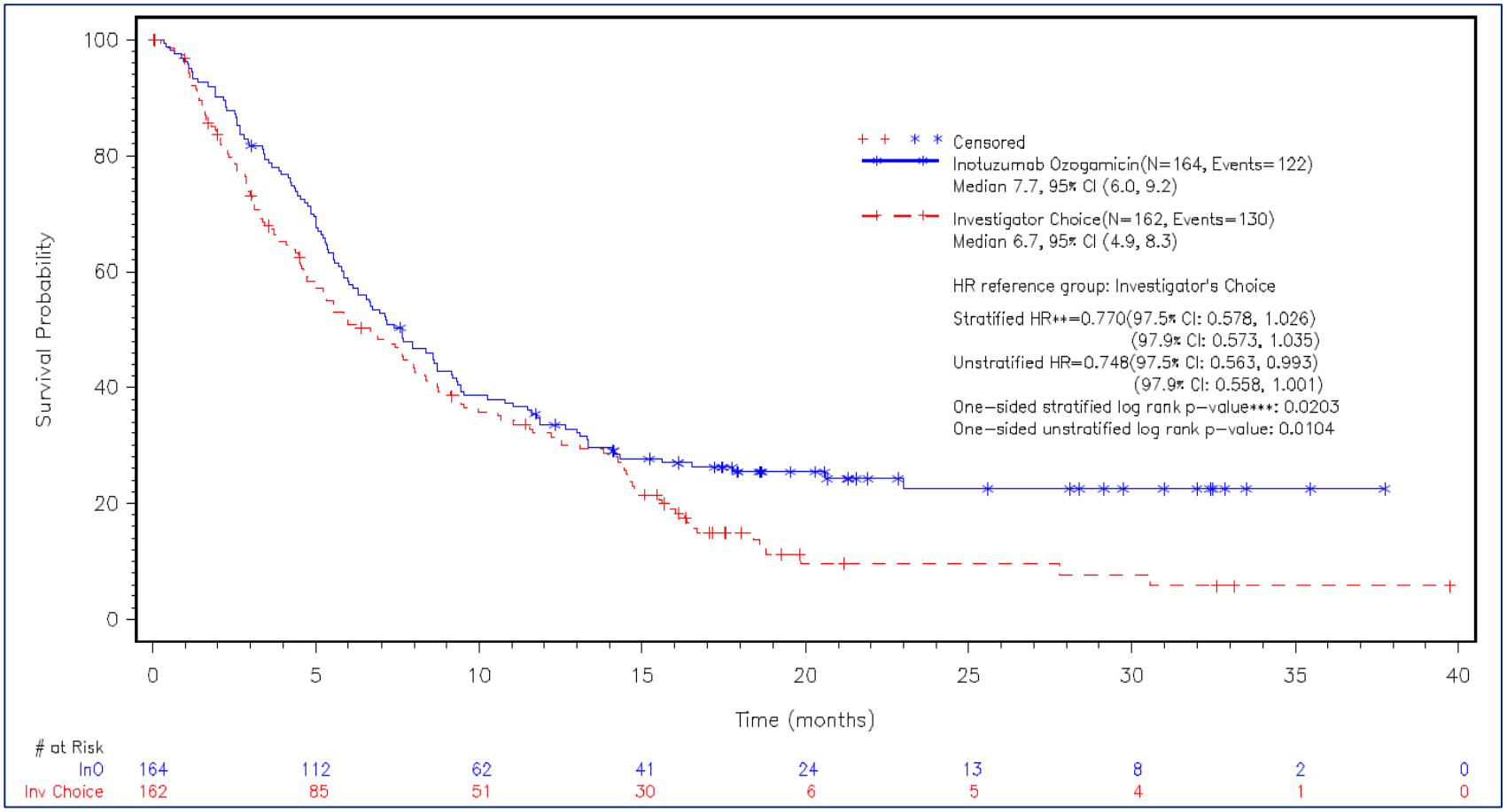
- CR/CRi assessed by an independent Endpoint Adjudication Committee for ITT218, and by the trial investigators for the full ITT population.
- results were broadly similar

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery.

INO-VATE1022: overall survival (I)

Kaplan–Meier plot of overall survival (ITT population):

- The INO-VATE 1022 trial did not meet its second primary objective of significantly (prespecified p=0.0208) longer OS in the inotuzumab vs SoC



Key: # at risk, number at risk; CI, confidence interval; HR, hazard ratio; Inv Choice, investigator's choice of chemotherapy.

INO-VATE1022: overall survival (II)

Truncation time tau (months)	RMST (months) (95 % CI)		RMST Difference (95% CI)	1-sided P-value
	Inotuzumab N=164	SoC N=162		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS months (95% CI)	7.7 (6.0, 9.2)	6.7 (4.9, 8.3)	-	-
Deaths n (%)	122 (74.4)	130 (80.2)	-	-
Censored n (%)	42 (25.6)	32 (19.8)	-	-

Key: CI, confidence interval; OS, overall survival; RMTL, restricted mean time lost; SoC, standard of care.

INO-VATE1022: overall survival (III)

OS by MRD status in CR/CRi patients treated with Inotuzumab:

By treatment:

- Patients with MRD negativity: median OS of [redacted] months for [redacted] patients and [redacted] months for [redacted] patients in inotuzumab and SoC respectively
- Patients without MRD negativity: [redacted] months median OS for [redacted] and [redacted] patients in inotuzumab and SoC respectively.

Key: MRD, minimal residual disease; OS, overall survival.

INO-VATE1022: Subsequent HSCT (I)

ITT	Inotuzumab (N = 164)	SoC (N = 162)
Patients with HSCT, n (%) [95% CI]	[redacted]	[redacted]
• Difference (95% CI) [p-value]	[redacted]	
Including patients with intervening induction therapy before receiving HSCT		
Did not have HSCT	[redacted]	[redacted]
• Achieved CR/CRi	[redacted]	[redacted]
• Did not achieve CR/CRi	[redacted]	[redacted]
Had HSCT	[redacted]	[redacted]
HSCT and CR/CRi	[redacted]	[redacted]
HSCT but not CR/CRi	[redacted]	[redacted]

The model grouped all HSCT patients together, regardless of CR/CRi status

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; MRD, minimal residual disease SoC, standard of care.

INO-VATE1022: Subsequent HSCT (II)

- **OS following HSCT:**

Key: HSCT, haematopoietic stem cell transplant; OS, overall survival.

INO-VATE1022: PFS (I)

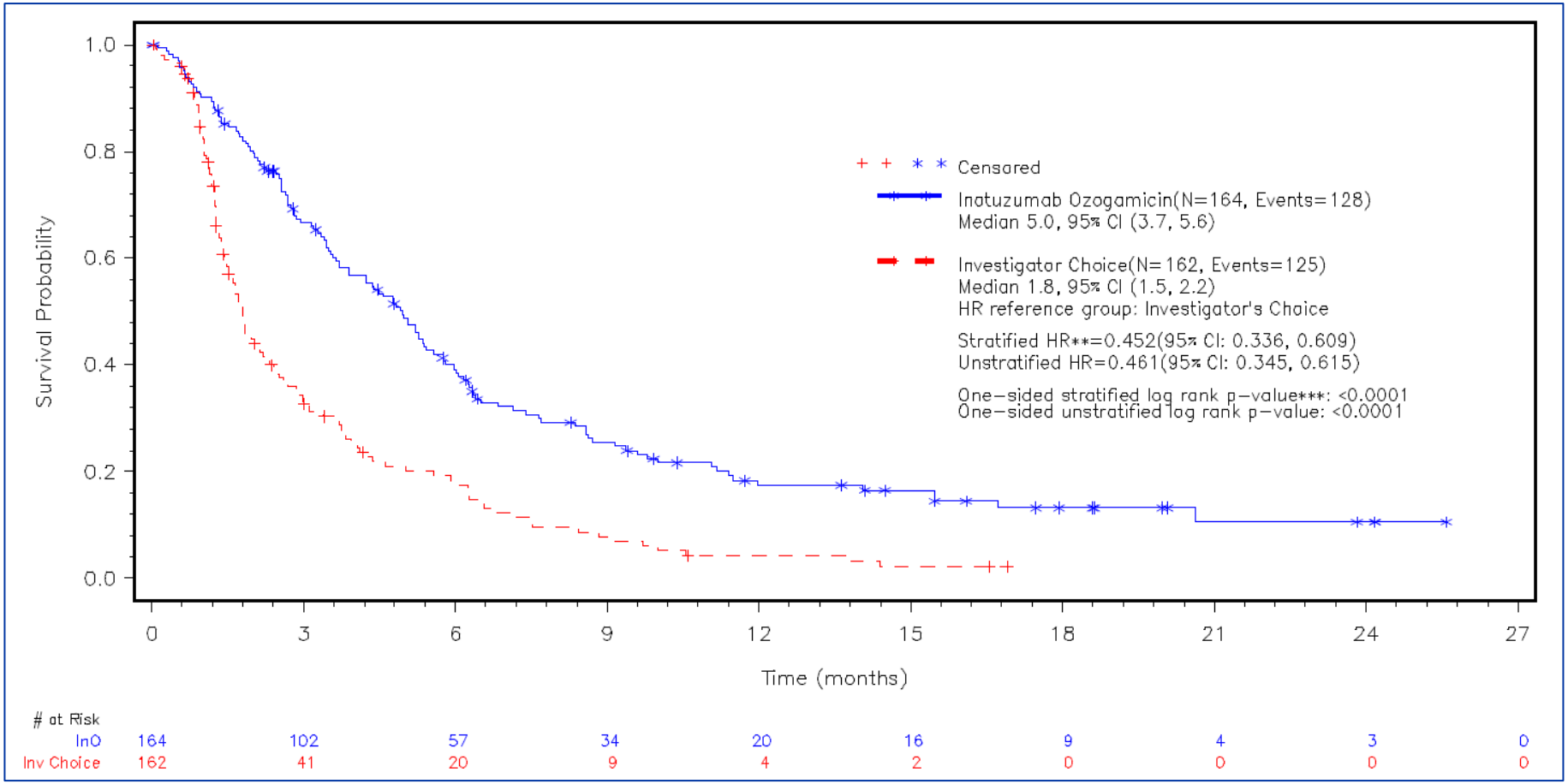
PFS = time from randomisation to: death, progressive disease, or starting a new induction therapy or post-therapy HSCT without achieving CR/CRi.

	Inotuzumab (N = 164)	SoC (N = 162)
Total patients with events, n (%)	128 (78.0)	125 (77.2)
• **Death**	[redacted]	[redacted]
• **Objective progression**	[redacted]	[redacted]
• **Relapse from CR/CRi**	[redacted]	[redacted]
• **Treatment discontinuation**	[redacted]	[redacted]
• **Starting new induction therapy or post-therapy HSCT without achieving CR/CRi**	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	5.0 (3.7, 5.6)	1.8 (1.5, 2.2)
Stratified HR (97.5% CI) [p-value]	0.452 (0.336, 0.609) [<0.0001]	
Unstratified HR (97.5% CI) [p-value]	[redacted]	

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; InO, inotuzumab ozogamicin; PFS, progression-free survival; SoC, standard of care.

INO-VATE1022: PFS(II)

Kaplan–Meier plot of progression-free survival (ITT population)



Key: CI, confidence interval; HR, hazard ratio; Inv, investigator; ITT, intent-to-treat; IVRS, Interactive Voice Response System.

INO-VATE1022: SoC OS and PFS

- **SoC**: [redacted] out of the 162 patients were randomised but were not treated (0 out of 164 in inotuzumab arm were untreated):
  - would be categorised as not achieving CR/CRi
  - were excluded and safety population is considered in model (not ITT)

[redacted]

Key: OS, overall survival; PFS, progression-free survival; SoC, standard of care.

INO-VATE1022: EQ5D-3L

Mean (SE/95%CI)	Inotuzumab (N = 164)	SoC (N = 162)
ITT population baseline		
EQ-5D Index[b]	[redacted]	[redacted]
EQ-VAS[c]	[redacted]	[redacted]
ITT population 8 March 2016 data cut		
EQ-5D Index	[redacted]	[redacted]
Inotuzumab – SoC EQ-5D Index [d]	[redacted]	
EQ-VAS	[redacted]	[redacted]
Inotuzumab – SoC EQ-5D VAS [d]	[redacted]	

Key: EQ-5D, EuroQoL 5 Dimension questionnaire; SE, standard error; SoC standard of care.

INO-VATE1022: Adverse Events

	All cycles		Cycle 1 only	
Safety population n (%)	Inotuzumab (N=164)	SoC (N=143)	Inotuzumab (N=164)	SoC (N=143)
Number of AEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
Temp. discontinued due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
Temp. discount. & dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Veno-occlusive disease (VOD)	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]

- The average number of cycles was 3 and 1 in inotuzumab and SoC respectively
- VOD rates were particularly high in Japanese centres; VOD in non-Japanese patients formed the model base case

Key: AE, adverse event; SAE, severe adverse event; SoC, standard of care.

ERG comments: INO-VATE 1022 design

Evaluation of inotuzumab based on a reasonably good quality RCT.

Population: broadly applicable to patients seen in NHS

- Included R/R CD22-positive ALL due to have Salvage 1 or 2 therapy and for which either arm of randomised therapy was a reasonable option
- patients who would be treated with BSC and patients due to receive Salvage 3+ not eligible
- The full ITT population results are the most relevant; more complete than the ITT218 population (results broadly similar)
- The average age (47 years) < than in NHS practice, thus reported survival rates may be higher than in NHS

Investigator's choice of SOC

- CM and HIDAC not used in current NHS practice
- most received FLAG-based chemotherapy, which is used in NHS

Key: ALL, Acute lymphoblastic leukaemia; R/R, relapsed and refractory; FLAG, Fludarabine, cytarabine and granulocyte-colony stimulating factor (GCSF) based combination chemotherapy; CM, cytarabine plus mitoxantrone; HIDAC, high dose cytarabine ; SoC, standard of care.

ERG comments: INO-VATE 1022 results

CR/CRi

- [redacted] inotuzumab & [redacted] SoC patients had CR/CRi, and [redacted] inotuzumab & [redacted] SoC patients had HSCT.
- But [redacted] inotuzumab and [redacted] SoC patients had HSCT despite not achieving CR/Cri, and [redacted] inotuzumab and [redacted] SoC patients did not receive HSCT, despite achieving CR/CRi.

OS data

- The post-hoc RMST analyses depend [redacted]
- The company RMST analysis truncated at 37.7 months with median OS 13.9 and 9.9 months for inotuzumab and SoC respectively
- The SoC OS estimate is higher than estimates for R/R B-cell ALL: range 3 to 5 months (CS Table 6, page 54) suggesting inflated SoC OS

VOD

- [redacted] in inotuzumab & [redacted] in SoC; only non-Japanese VOD modelled.

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplant; OS, overall survival; RMST, restricted mean survival time; SoC, standard of care; VOD, Veno-occlusive disease.

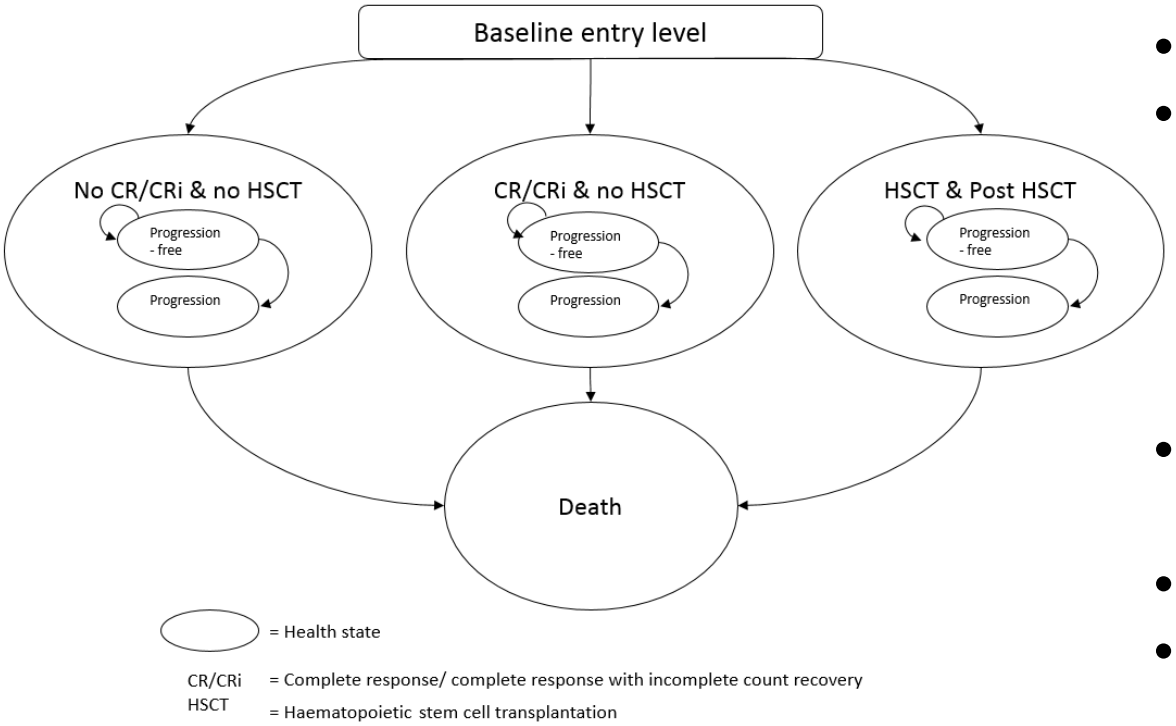
Clinical effectiveness and treatment pathway issues

1. How would inotuzumab fit into the current treatment pathway?
   - What are the appropriate comparators? Are clofarabine and TKIs alone relevant comparators for some people?
   - Can inotuzumab be used in outpatient setting?
2. Is the “fit for treatment” population in INO-VATE 1022 reflective of NHS practice?
3. What is the prognosis for relapsed or refractory ALL?
4. The INO-VATE 1022 trial compared inotuzumab with investigator’s choice (SoC). Is SoC reflective of NHS practice?
5. How generalisable are INO-VATE 1022 results?
   - What is the most relevant population, ITT, ITT218, safety population?
   - Are RMST OS analyses appropriate?
   - Not all CR/CRi patients in INO-VATE 1022 had HSCT and some had HSCT without CR/CRi

Cost-effectiveness evidence

Company's model

- Partitioned survival model with 4 health states (safety population)
- tunnel states within HSCT & post HSCT represent the wait for HSCT
- Sub states for progression free and progressed disease
- PFS and OS modelled using covariates (safety population)



- UK NHS perspective
- Costs and QALYs discounted at an annual rate of 1.5% (base case) and 3.5% (scenario analyses)
- Cycle = 28 days + half cycle correction
- Lifetime horizon = 60ys
- Starting age = 46 (ITT)

Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant. **Note**: Patients receiving HSCT (after entry to the model) enter the 'HSCT and Post HSCT' partitioned survival sub-model, whether or not they achieve CR or CRi.

Company's model - summary

Clinical data	INO-VATE 1022 (safety population)
Assumption	Patients' response to treatment is determined within 1 cycle: all patients enter in Cycle 0 = baseline entry level (first cycle) and transition during Cycle 0…
Comparators	• SoC = FLAG-IDA and FLAG + imatinib for Ph+ patients (based on INO-VATE 1022 SoC of FLAG, CM and HIDAC). • Efficacy assumption: FLAG = FLAG-IDA = FLAG + imatinib thus only cost added
Utilities	Progression free • No CR/CRi and no HSCT and CR/CRi and no HSCT: INO-VATE 1022 • HSCT & post HSCT: treatment independent, based on time post HSCT: Kurosawa et al. 2016 Progressed patients: Aristides et al. 2015
AE	• AE accounted for in the on-treatment utility • disutility for veno-occlusive disease (VOD; 0.208) • GvHD captured in post-HSCT utilities from Kurosawa et al. 2016
Cure point	Patients alive after 3 years cured - life expectancy = normal population
Cost	drug acquisition and administration costs (cost for idarubicin and imatinib added), cost of HSCT, costs of AE, cost of induction treatments, and terminal care costs
Discount	1.5% for utilities and costs (base case).

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplant; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor therapy; FLAG-IDA, FLAG and idarubicin; GvHD, graft versus host disease; CM, Cytarabine plus mitoxantrone; HIDAC, high dose cytarabine; SoC, standard of care.

Company's model - health states

Proportion of patients in each health state from Cycle 1

Health state	Inotuzumab	SoC
No CR/Cri and no HSCT	[redacted]	[redacted]
CR/CRi and no HSCT	[redacted]	[redacted]
HSCT and post-HSCT	[redacted]	[redacted]

- [redacted] of inotuzumab and [redacted] of SoC patients receiving HSCT received their HSCT prior to any post induction therapy
- Tunnel states: INO-VATE 1022 waiting time to receive HSCT up to [redacted] cycles for inotuzumab and [redacted] cycles for SoC
  - scenario analyses explored a maximum of 3 cycles (all patients receiving HSCT after cycle 3 are assumed to receive it in cycle 3)

Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant.

Company's model - PFS and OS

Health state		Parametric curve	Goodness of visual fit	Best statistical fit	Clinically plausible
No CR/CRi & no HSCT	OS	Log-logistic	Yes	No	Yes
	PFS	Log-logistic	Yes	Yes	Yes
CR/CRi & no HSCT	OS	Log-logistic	Yes	Yes	Yes
	PFS	Log-normal	Yes	Yes	Yes
HSCT & Post-HSCT	OS	Gompertz	Yes	Yes	Yes
	PFS	Gompertz	Yes	No	Yes

- Same parametric curves applied to both arms
- Covariates: treatment, age, duration of first remission, salvage status, Ph-status, prior HSCT, region
- OS K-M data:
  - *No CR/CRi & no HSCT*: [redacted]* & [redacted]* years for inotuzumab & SOC (complete)
  - *CR/CRi & no HSCT*: [redacted] & [redacted] years for inotuzumab & SOC
  - *HSCT & post HSCT*: [redacted] & [redacted] years for inotuzumab & SoC

Key: *, estimated from figure 30 and 3 CS page 177 and 178 CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care.

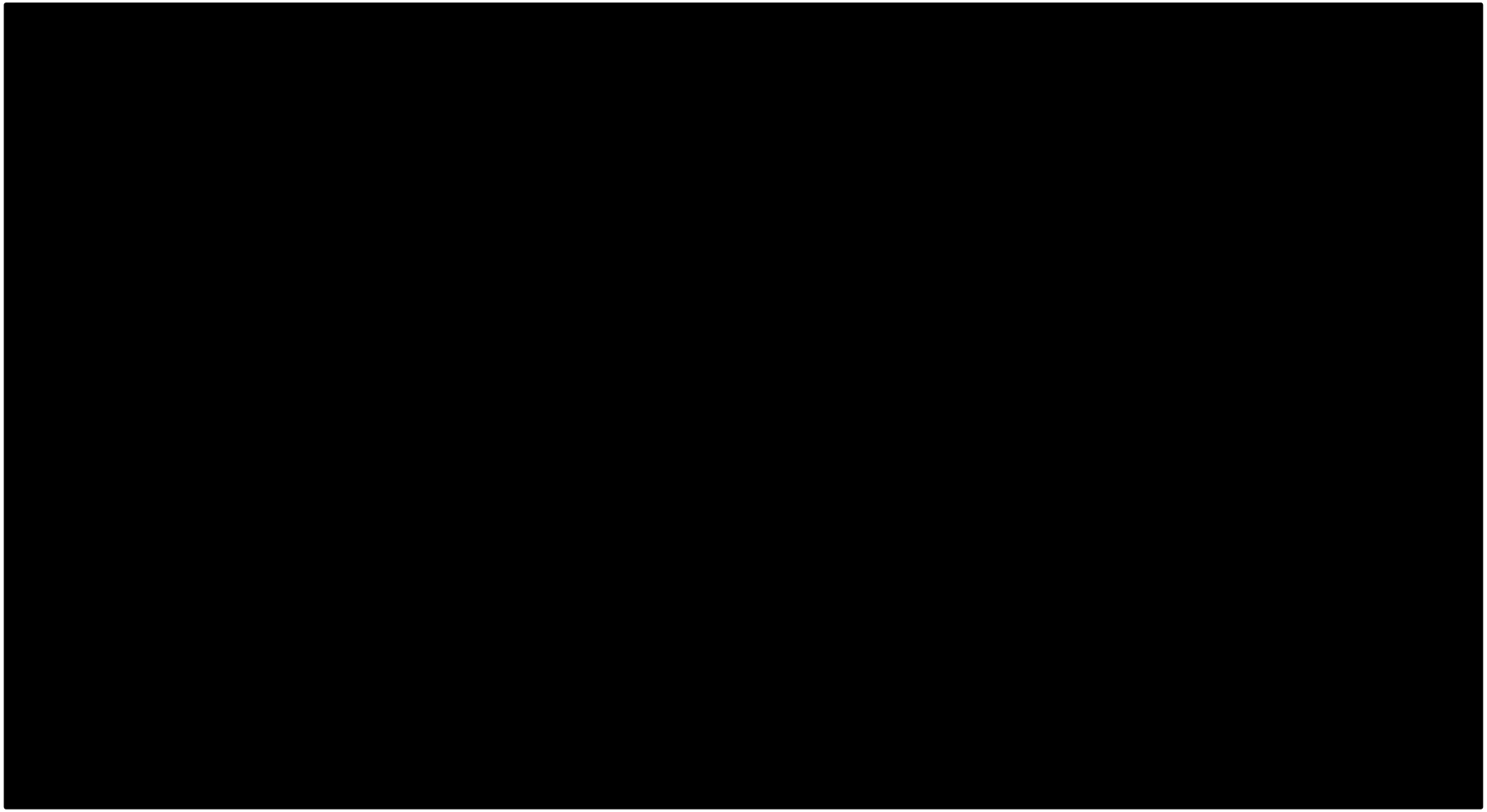
Company's model – HSCT and post HSCT parametric OS curves

- Gompertz curves (light blue) selected to represent OS in HSCT & Post HSCT state up to cure point (3 years)

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care.

Company's model: OS in HSCT & post HSCT

- General population age-specific mortality rates used after cure point (3 years)



Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; RMST, restricted mean survival time; SoC, standard of care.

Company's model – Cure post-HSCT

Base case:

3 years cure point (most clinically plausible)

- Inotuzumab: [redacted] and SOC: [redacted] post-HSCT patients alive at this point (based on the fitted Gompertz curves)
- Mortality becomes the same as the general population (age and gender matched to INO-VATE 1022)

- Other explored cure points

→ 5 years:

- Inotuzumab: [redacted] post-HSCT patients alive at this point
- SOC: [redacted] post-HSCT patients alive (at 4 years [redacted] alive)

→ 2 years:

- Inotuzumab: [redacted] post-HSCT patients alive at this point
- SOC: [redacted] post-HSCT patients alive

ERG comments: *HSCT & post HSCT* state

- Approximately 95% of QALY gain conferred in *HSCT & Post HSCT*
  - The majority of the differences in PFS, OS and hence QALYs are derived after the follow-up period of the trial
- [redacted] in RMST for patients achieving CR/CRi in *HSCT & Post HSCT*
- Small number of patients in *HSCT & Post HSCT* state and this subgroup is not randomised
- Uncertainty around the company "cure point" of 3 years post HSCT
  - survival gains estimated at 3 years are extrapolated over a lifetime.
- Mortality rate after HSCT does not equal to general population
  - mortality improves in 5 years after HSCT, but remains 4-9 times higher for at least 25 years thereafter (Martin et al. 2011)
- ERG suggests pooling OS for *HSCT & Post-HSCT* state → as in Appendix 7 CS scenario analysis with MRD status covariate adjustment

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; MRD, Minimal residual disease; PFS, progression-free survival; RMST, restricted mean survival time; SoC, standard of care.

Company's model – treatment costs

Drug acquisition cost

Drug acquisition cost		Cost	%patients	Total cost	Total vials
SOC	FLAG-IDA	[redacted]	[redacted]		[redacted]
	CM	[redacted]	[redacted]	[redacted]	[redacted]
	HIDAC	[redacted]	[redacted]		[redacted]
	TKI (Imatinib) Ph+ patients	[redacted]	[redacted]		[redacted]
Inotuzumab				[redacted]	[redacted]

Administration cost

- SOC: the average length of inpatient stay was [redacted] days and the total cost per patient for the average course of treatment was **£4,632.81**
- Inotuzumab: the average length of treatment was [redacted] cycles and the total cost per patient for the average course of treatment was **£2,582.80**

Key: CM, cytarabine plus mitoxantrone; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin; HIDAC, high dose cytarabine; SoC, standard of care; TKI, tyrosine kinase inhibitor

Company's model – salvage treatments and HSCT costs

Cost of subsequent induction therapies:

- Salvage therapies based on INO-VATE 1022 ITT (not all therapies included: CAR-T cell therapy, grow factors, [redacted]
- Inotuzumab**: £7,625** and SOC: **£19,199** (average costs per cohort member)

Cost of HSCT (only for those patients receiving HSCT):

Type of cost	Cost in NHS reference before inflation indices	Cost per cycle	Source
SCT cost	£58,903	**£60,891.72**	NHS blood and transplant (2014) uplifted from 2012/2013 to 2015/2016 prices using PSSRU inflation indices. (297.0/287.3)
Post-HSCT			
Post-HSCT in first 6 months	£28,390	**£4,891.42**	
Post-HSCT from 6–12 months	£19,502	**£3,360.07**	
Post-HSCT from 12–24 months	£14,073	**£1,212.35**	

Key: NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HSCT, haematopoietic stem cell transplant

ERG comments: treatments and salvage therapy

- Clofarabine and imatinib alone not included as comparators
- Added cost of idarubicin and imatinib, but same efficacy assumed (FLAG = FLAG-IDA = FLAG & imatinib)
  - Exclude these costs to ensure consistency between the efficacy outcomes and cost assumptions
- Cost of subsequent therapies = a positive bias towards inotuzumab
  - Cost derived from the ITT, not safety population
  - More patients in SoC had subsequent induction
  - inclusion of these costs potentially inappropriate
- Administration cost for inotuzumab
  - Modelled in outpatient setting: this does not reflect UK clinical setting
  - [redacted] inotuzumab patients were hospitalised during Cycle 1 should be based on INO-VATE 1022

Key: FLAG, Fludarabine, cytarabine and granulocyte-colony stimulating factor (GCSF) based combination chemotherapy; CM, cytarabine plus mitoxantrone; HIDAC, high dose cytarabine.

Company's model - utilities

State		Utility value: mean (SE)	95% CI	Source
Baseline		InO: 0.69 (0.02) SoC: 0.67 (0.03) *Pooled: 0.69 (0.02)**	0.65–0.74 0.62–0.73 -	INO-VATE 1022
No CR/CRi & no HSCT		[redacted]	[redacted] -	
CR/CRi & no HSCT		[redacted]	[redacted] -	
Post-HSCT	**<1 year post**	0.59 (0.10)	0.40–0.78	AML utilities from Kurosawa 2016 (include GvHD disutility)
	1–2 years' post	0.75 (0.03)	0.69–0.82	
	3–5 years' post	0.74 (0.02)	0.70–0.78	
	>5 years post	0.76 (0.03)	0.71–0.81	
Progression		0.30 (0.04)	0.22–0.38	Aristides 2015
VOD after HSCT applied for 1 cycle		0.208	-	acute liver failure pretransplant. (SMC)

Key: *, used in sensitivity analyses; SoC, standard of care; InO, inotuzumab; HSCT, haematopoietic stem cell transplant; VOD, veno-occlusive disease.

ERG comments: utilities

- INO-VATE 1022
  - open-label design introduces potential bias for subjective outcomes (HRQL)
  - pooled utility values may be more appropriate

- *HSCT & Post-HSCT*
  - utilities derived using Japanese value set
  - over the 60-year lifetime horizon values exceed general population estimates declining with age
  - utilities should be further adjusted for age

- Disease progression
  - 0.3 applied to progression in all 3 model states
  - progression is assumed to influence HRQL but does not impact OS (cure point = general population mortality)
  - large impact on the estimated QALY gains as the model predicts progression in [redacted] and [redacted] of patients with HSCT following SoC and inotuzumab respectively

Key: HRQL, Health-related quality of life; HSCT, haematopoietic stem cell transplant; OS, overall survival; QALY, quality adjusted life years.

Company's model - adverse events

Adverse event	Inotuzumab	SoC	Source
Adverse events on treatment			
Neutropenia	[redacted]	[redacted]	INO-VATE 1022
Thrombocytopenia	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	
Febrile neutropenia	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	
Lymphopenia	[redacted]	[redacted]	
White blood cells decreased	[redacted]	[redacted]	
Veno-occlusive liver disease	[redacted]	[redacted]	
Adverse events post-HSCT			
Veno-occlusive liver disease in non-Japanese patients (base case)	[redacted]	[redacted]	INO-VATE 1022 (safety population)
Veno-occlusive liver disease	[redacted]	[redacted]	
GvHD: not treatment specific	11.34%	11.34%	Kiehl et al. 2004

Key: SoC, standard of care; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; VOD, veno-occlusive disease.

Company's model - AE costs

AE (average costs per patients in the entire cohort)

- Grade ≥3 and experienced by ≥5% of INO-VATE 1022 patients included

Treatment	AE cost on treatment	AEs post-HSCT	Total
Inotuzumab	**£2,622.50**	£11,088.67	£13,711.17
SoC	**£1,239.23**	£689.45	£1,928.68

- episode costs:
  - GvHD from Espérou et al. 2004 (converted to GBP and inflated to current prices) assumed not to be treatment specific: **£26,888.92**
  - VOD (treatment with defibrotide; SMC 2014): **£113,432.00**

Disease monitoring

- assumed to be captured in the outpatient/inpatient visit for administration and the adverse event costs. No further health-state unit or resource use costs were applied.

Terminal care

- **£11,616** is applied to patients upon death. It is assumed that this cost also incorporates the cost of treating a progressed patient (PSSRU 2016).

Key: AE, adverse event; HSCT, haematopoietic stem cell transplant; GvHD, graft versus host disease; SoC, standard of care; VOD, veno-occlusive disease.

Company's base case

Deterministic results

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
Costs and benefits discounted at 1.5%							
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£40,013
SoC	[redacted]	[redacted]	1.49				
Costs and benefits discounted at 3.5%							
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£55,869
SoC	[redacted]	[redacted]	1.49				

Probabilistic results

	Incremental			ICER
	Costs	QALYs	LYs	
Costs and benefits discounted at 1.5%				
Inotuzumab vs SoC	[redacted]	[redacted]	4.69	£48,459
Costs and benefits discounted at 3.5%				
Inotuzumab vs SoC	[redacted]	[redacted]	4.70	£67,575

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.
Note: results do not include fix provided by company during clarification process.

Company's base case: QALY by health state

Summary of discounted QALY gain by health state (1.5% discount)

Health state	QALY inotuzumab	QALY SoC	Increment
No CR/CRi	[redacted]	[redacted]	[redacted]
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]
HSCT & Post HSCT	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

- the majority of the QALY gain is conferred within the *HSCT & Post HSCT* state

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; QALY, quality-adjusted life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Company's probabilistic sensitivity analysis (discount rate of 1.5%)

At a £50,000 WTP threshold, the probability that inotuzumab is a cost-effective treatment option versus SoC is 45% for a discount rate of 1.5%

Key: ICER, incremental cost-effectiveness ratio; PSA, patient access scheme; QALY, quality-adjusted life year.
Note: results do not include fix provided by company during clarification process

Company's Tornado diagram (discount rate of 1.5%) –10 most influential parameters

The ICER was most sensitive to the cost of HSCT, choice/cost of subsequent induction treatments and the utility of progressive disease.

Key: ICER, incremental cost-effectiveness ratio; PSA, patient access scheme; QALY, quality-adjusted life year
Note: results do not include fix provided by company during clarification process

Deterministic sensitivity analysis (discounted at 1.5%)

Input	Scenario	ICER
Base case		£40,013
Reflective of UK clinical practice	Max 3 cycles, as per SPC	£34,311
	No prior HSCT	£37,382
Comparator	All FLAG-IDA in SoC	£39,027
	All CM in SOC	£41,714
	All HIDAC in SOC	£42,101
Utilities from UK HTA in ALL	utility from the blinatumomab SMC	£35,660
Post HSCT cure point (base case 3 years)	2 years	£44,464
	5 years	£39,301
Cost of HSCT	No costs of HSCT applied	£30,576
Time to HSCT (tunnel states)	Up to 3 cycles	£40,084
	Average time to HST	£37,515
Age adjusted utilities	Age adjusted utilities	£43,909
Discount rate	QALYs 1.5%, Costs 3.5%	£39,473
	QALYs 3.5%, Costs 3.5%	£55,869
Time horizon	5 years	£253,651
	10 years	£130,513
	20 years	£70,333
	30 years	£51,174

ERG comments: summary

- Clofarabine and imatinib alone not modelled
- The use of the INO-VATE 1022 safety population is appropriate
- Absence of a structural link between CR/CRi and HSCT
- Splitting INO-VATE 1022 & fitting multiple parametric curves is too complex
- Inotuzumab mortality benefit in HSCT & post HSCT is uncertain
  - post HSCT mortality can be 4-9 x higher than general population
  - when to switch from modelled to population mortality is uncertain
- Cost and QALY's discount rate of 1.5% is not appropriate
- Adding the cost of idarubicin and imatinib is not appropriate
- Cost of subsequent therapies = positive bias towards inotuzumab
- Administration cost for inotuzumab should be based on INO-VATE 1022
- Utilities should be age adjusted
- On-treatment utilities should be pooled

Key: ALL, Acute lymphoblastic leukaemia; R/R, relapsed and refractory; SoC, standard of care.

Additional ERG analyses (discounted at 3.5%)

- Fix to base case provided by company during clarification process **(1)**
- Pooling survival data post HSCT with an adjustment for MRD- and treatment specific rates of MRD- for patients with remission (CS scenario analysis) **(2)**
- Non-parametric approach using KM data and cure point of 2,75 years with pooled (7a) or separate (7b) curves post HSCT **(7)**
- Age adjusted utilities (CS scenario analysis) **(3)**
- Pooled on treatment utilities (CS scenario analysis) **(5)**
- Cost of subsequent therapy (blinotumab & inotuzumab) replaced with cost of chemotherapy (CS scenario analysis) **(6)**
- Removing cost of imatinib and idarubicin from SoC **(4)**
- Administration cost for inotuzumab as per INO-VATE-022 **(9)**
- 4-fold risk of mortality post cure **(8)**

ERG non-parametric base case (1+3+4+5+6+7a+8+9)

ERG parametric base case (1+2+3+4+5+6+8+9)

Key: CS, company submission; HSCT, haematopoietic stem cell transplant; MRD-, minimal residual disease negativity; SoC, standard of care.

Comparison of OS in INO-VATE 1022, CS submission and ERG analysis

OS at 3 years: Company base case: [redacted] for inotuzumab and [redacted] SoC
ERG non-parametric: [redacted] for inotuzumab and [redacted] SoC
ERG parametric: [redacted] for inotuzumab and [redacted] SoC

[redacted]

Key: OS, Overall survival; K-M; Kaplan-Meier; SoC, standard of care.

Additional ERG analyses (3.5% discount)

Scenario (ERG analysis)	Inc. cost	Inc. QALY	ICER	Change
Company base case (3.5% discount)	[redacted]	[redacted]	£55,869	-
Company corrected base case (1)	[redacted]	[redacted]	**£55,779**	-£90
CS scenario pooled OS with MRD (2)	[redacted]	[redacted]	£77,783	+£21,914
KM OS & pooled post-HST (7a)	[redacted]	[redacted]	£83,060	+£27,191
KM OS & separate post-HST (7b)	[redacted]	[redacted]	£56,483	+£614
Age adjusted utilities (3)	[redacted]	[redacted]	£60,260	+£4,391
Pooled on treatment utilities (5)	[redacted]	[redacted]	£55,992	+£123
Chemo as subsequent therapy (6)	[redacted]	[redacted]	£61,594	+£5,725
Imatinib & IDA cost removed (4)	[redacted]	[redacted]	£57,287	+£1,418
Inotuzumab administration cost (9)	[redacted]	[redacted]	£57,804	+£3,165
post HSCT 4-x mortality risk (8)	[redacted]	[redacted]	£68,381	+£12,512
ERG non-parametric base case	[redacted]	[redacted]	**£122,174**	+£66,305
ERG parametric base case	[redacted]	[redacted]	**£114,078**	+£58,299

Company: End of life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Adults with R/R ALL experience reported median OS as low as 3 months with current therapies. • Median OS in INO-VATE 1022 for SoC (representative of UK clinical practice) is 6.7 months using the primary OS analysis and 9.9 months for the RMST analysis.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Using the RMST analysis, inotuzumab significantly extends OS to 13.9 months vs 9.9 months with chemotherapy (p=0.0023), for a gain in OS of 4-months with a limited 37.7 months of follow-up. • The economic model presents mean life years for SoC as 1.49 and 6.66 for inotuzumab, showing an increase greater than the 3 months.

ERG:

- The life expectancy for R/R B-cell ALL adult patients is around 3-6 months.
- Although the survival benefits of inotuzumab are subject to high uncertainty, it is likely that by increasing the rate of HSCT, inotuzumab will increase the mean survival for patients with R/R B cell ALL by more than 3 months.

Key: OS, overall survival; RMST, restricted mean survival time; SoC, standard of care.

Company: Innovation

Inotuzumab represents a step-change in disease management in a population for whom there is a poor prognosis, significant unmet need and limited treatment options

- **Improved efficacy**
  - demonstrates significant improvements in minimal residual disease (MRD) negativity, and health-related quality of life (HRQL) outcomes, and a meaningful survival benefit versus chemotherapy
- **Novel mode of action and improved safety profile**
  - utilises a novel, targeted mode of action to limit systemic toxicity in the destruction of cancer cells, which means that it is well-tolerated and has a manageable safety profile compared to other chemotherapy agents.
- **Improved administration**
  - convenient administration schedule, with no requirement for hospitalisation to receive treatment, and with reduced hospitalisations for management of disease and AEs due to its improved superior efficacy and safety profile.

Equality issues

- No equality or equity issues were identified by the company or the ERG

Cost-effectiveness issues

1. Is 1.5% cost and QALY's discount rate appropriate for decision making?
2. OS data
   - Is the OS modelling in the *HSCT & Post-HSCT* state appropriate
   - Is the assumption of the "cure point" at 3 years appropriate?
   - What is the mortality rate after HSCT?
3. Cost
   - How should be the administration cost of inotuzumab modelled?
   - Is it appropriate to add the cost of idarubicin and imatinib to the cost of SoC?
   - Should the cost of subsequent therapies be included in the model?
4. Were appropriate utilities used in the model?
5. Are the end-of-life criteria met?
6. What is the most plausible ICER?

Authors

- **Marcela Haasova**
  Technical Lead
- **Sally Doss**
  Technical Adviser
- with input from the Lead Team (Mike Chambers, John Hampson and David Chandler)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of inotuzumab ozogamicin within its marketing authorisation for treating relapsed or refractory B-cell acute lymphoblastic leukaemia.

Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL and T-cell ALL. B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 20–30% of adults with ALL. The disease is described as Philadelphia-chromosome-positive if the abnormality is present, and Philadelphia-chromosome-negative if it is not present.

ALL is most common in children, adolescent and young adults, with 65% of cases diagnosed in people aged under 25 years. A second increase in incidence is observed in people aged over 60 years. In England, 820 people were diagnosed with ALL in 2013 and 240 people died from ALL in 2014.

The aim of treatment in ALL is to achieve a cure. Treatment for newly diagnosed ALL can take up to 3 years to complete and is generally divided into 3 phases; induction phase, consolidation and maintenance. Although selection of drugs, dose schedules and treatment duration may differ slightly between different subtypes of ALL, the basic treatment principles remain similar. During induction, newly diagnosed ALL is generally treated with chemotherapy combinations including prednisone, vincristine, anthracycline and asparaginase. NICE technology appraisal guidance 408 recommends pegaspargase (pegylated asparaginase), as part of antineoplastic combination therapy, as an option for untreated newly diagnosed acute lymphoblastic leukaemia in children, young people and adults. During the consolidation phase, intensified chemotherapy is used, which may include high dose methotrexate with mercaptopurine, high dose asparaginase, or a

repeat of the induction therapy. During the maintenance phase low dose chemotherapy is used, which typically consists of weekly methotrexate and daily mercaptopurine for an extended period of time to prevent relapse. For people with Philadelphia-chromosome-positive ALL, tyrosine kinase inhibitor therapy is added to these chemotherapy regimens. In adults with high risk acute ALL, stem cell transplantation and chemotherapy are considered equal first line treatment options.

Relapse or becoming refractory to initial treatment occurs in approximately 45% of people with newly diagnosed B-cell ALL. Although there is currently no standard of care for people with relapsed or refractory ALL, possible treatment options may include a combination chemotherapy based regimen of fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG), followed by stem cell transplantation where a suitable donor can be found, or best supportive care (including palliative care). Clofarabine is used outside its marketing authorisation in clinical practice in England through the Cancer Drugs Fund (CDF) for people with relapsed or refractory ALL 'with intent to use the treatment to bridge to bone marrow transplant' (at the time the scope was written; CDF transition funding remains in place until a commissioning decision from NHS England). Treatment of relapsed Philadelphia-chromosome-positive ALL includes re-induction therapy with tyrosine kinase inhibitors, such as imatinib or dasatinib, in addition to FLAG- or clofarabine-based chemotherapy.

The technology

Inotuzumab ozogamicin (Besponsa, Pfizer) is an antibody-drug conjugate of a monoclonal antibody. When inotuzumab ozogamicin binds to a CD22 antigen on a B-cell, it is absorbed into a malignant cell and leads to cell death.

Inotuzumab ozogamicin does not currently have marketing authorisation in the UK for ALL. It has been studied in clinical trials in adults with relapsed or refractory B-cell ALL with a CD22 expression.

Intervention(s)	Inotuzumab ozogamicin
Population(s)	Adults with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL)

Comparators	For people who are able to take chemotherapy and have
	• Philadelphia-chromosome-negative ALL:
	  ○ fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy
	  ○ clofarabine-based combination chemotherapy (not appraised by NICE but funded via the CDF).
	• Philadelphia-chromosome-positive ALL:
	  ○ tyrosine kinase inhibitors alone or in combination with FLAG- or clofarabine-based chemotherapy.
	For people who are unable to take chemotherapy:
	• best supportive care (including palliative care).

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • treatment response rates (including haematologic responses) • time to and duration of response • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	If the evidence allows, the economic analysis will include stem cell transplant as a subsequent treatment after inotuzumab ozogamicin or its comparators. This should reflect the proportion of people who proceed to allogeneic stem cell transplant after each treatment, as well as the costs and quality-adjusted life year benefits of the procedure. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Pegaspargase for treating acute lymphoblastic leukaemia (2016). NICE technology appraisal TA408. Review date TBC. **Terminated appraisals:** Dasatinib for the treatment of acute lymphoblastic leukaemia (terminated appraisal) (2008). **Appraisals in development:** Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia NICE technology appraisals guidance [ID671]. Publication expected June 2017. Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia asparaginase (suspended appraisal) NICE technology appraisals guidance [ID864]. Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia NICE technology appraisals guidance [ID804]. Publication date to be confirmed. **Related Guidelines:** Haematological cancers: improving outcomes (May 2016) NICE Guideline NG47. Review proposal date: September 2019. Suspected cancer: recognition and referral (June 2015). NICE guideline NG12. Improving outcomes in children and young people with cancer (August 2005). Cancer Service Guideline CGG7. Review decision: will be updated in July 2018.

	Related Quality Standards: Cancer services for children and young people (February 2014) NICE quality standard 55. Review date TBC. **Related NICE Pathways**: Blood and bone marrow cancers (2014) NICE Pathway (note that this pathway does not include acute lymphoblastic leukaemia).
Related National Policy	NHS England, Manual for prescribed specialised services 2016-2017, May 2016. Chapter 29 (Blood and marrow transplantation services (all ages)) and chapter 106 (Specialist cancer services for children and young people) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-2017, Apr 2016. Domains 1 and 2 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Department of Health, Improving Outcomes: A strategy for cancer, fourth annual report, Dec 2014. Department of Health, Cancer commissioning guidance, Dec 2009. NHS England, National Cancer Drugs Fund List, Sep 2016.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Inotuzumab ozogamicin for treating relapsed or refractory B cell acute lymphoblastic leukaemia [ID893]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Pfizer (inotuzumab ozogamicin) Patient/carer groups • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Muslim Council of Britain • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Accord Healthcare (cytarabine, filgrastim, fludarabine) • Allergan (fludarabine) • Amgen (filgrastim) • Bristol-Myers Squibb (dasatinib) • Chugai Pharma UK (lenograstim) • Hospira UK (cytarabine, filgrastim, fludarabine) • Novartis (imatinib) • Sandoz (filgrastim, fludarabine) • Sanofi (clofarabine, fludarabine) • Teva Pharma (lipegfilgrastim) Relevant research groups • Cochrane Haematological

Consultees	**Commentators (no right to submit or appeal)**
• British Society for Haematology • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Bedfordshire CCG • NHS Calderdale CCG • NHS England • Welsh Government	Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia [ID893]

Company evidence submission

February 2017

File name	Version	Contains confidential information	Date
ID893_Inotuzumab_Company submission_(08Feb17) ACiC	1.0	Yes	08 Feb 2017

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
AST	Aspartate transaminase
AWMSG	All Wales Medicines Strategy Group
BIA	Budget impact analysis
BIC	Bayesian information criterion
BMT	Bone marrow transplant
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CM	Cytarabine plus mitoxantrone
CNS	Central nervous system
CR	Complete response
CRh	Complete remission with partial haematological recovery
CRi	Complete response with incomplete count recovery
CRsg	Complete remission by study group
CSR	Clinical study report
CT	Chemotherapy
CU	Cost utility
CVAD	Cyclophosphamide, vincristine, Adriamycin and dexamethasone
DLI	Donor leukocyte infusion
DoR	Duration of remission
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDMC	External Data Monitoring Committee

Abbreviation	Definition
EMA	European Medicines agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-VAS	EuroQoL visual analogue scale
EQ-5D	EuroQoL 5 Dimension questionnaire
ESMO	European Society for Medical Oncology
FLAG	Fludarabine, cytarabine and granulocyte-colony stimulating factor
FLAM	Fludarabine, cytarabine and mitoxantrone
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
GvHD	Graft versus host disease
HCT	Haematopoietic cell transplant
HE	Health economic
HEAB	Hepatic Events Adjudication Board
HIDAC	High dose cytarabine
HR	Hazard ratio
HRQL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HSRIC	Horizon Scanning and Research Intelligence Centre
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDA	Idarubicin
InO	Inotuzumab ozogamicin
ITT	Intent-to-treat
IVRS	Interactive voice response system
KM	Kaplan–Meier
LFT	Liver function test
LY	Life Year
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRD	Minimal residual disease
NA	Not applicable
NHS	National Health Service
NIHR	National Institute for Health Research
NR	Not reported

Abbreviation	Definition
ONS	Office of National Statistics
OR	Odds ratio
OS	Overall survival
OWSA	One-way sensitivity analyses
pCODR	Pan-Canadian Oncology Drug Review
PD	Progressive disease
PFS	Progression-free survival
Ph+/-	Philadelphia-chromosome positive/negative
PR	Partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Parametric survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RMST	Restricted mean survival time
RR	Relapsed or refractory
RT	Radiotherapy
SAE	Severe adverse event
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
SPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TTO	Time trade-off
VOD	Veno-occlusive liver disease

Abbreviation	Definition
WBC	White blood cells
WTP	Willingness to pay

1. Executive summary

1.1 Statement of decision problem

The objective of this appraisal is to determine the clinical and cost effectiveness of inotuzumab ozogamicin (hereafter inotuzumab) within its anticipated marketing authorisation for adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL). Further details of the decision problem and how it has been addressed in this submission are presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory B-cell acute lymphoblastic leukaemia	Adults with relapsed or refractory B-cell acute lymphoblastic leukaemia	Not applicable
Intervention	Inotuzumab ozogamicin	Inotuzumab ozogamicin	Not applicable
Comparator (s)	For people who are able to take chemotherapy and have: • Philadelphia chromosome-negative (Ph-) ALL: o FLAG-based combination chemotherapy o clofarabine-based combination chemotherapy (not appraised by NICE but funded via the Cancer Drugs Fund) • Philadelphia chromosome-positive (Ph+) ALL o Tyrosine kinase inhibitors (TKIs) alone or in combination with FLAG- or clofarabine-based chemotherapy For people who are unable to take chemotherapy: • Best supportive care (including palliative care)	For people who are able to take chemotherapy and have: • Philadelphia chromosome-negative (Ph-) ALL: o FLAG-based combination chemotherapy • Philadelphia chromosome-positive (Ph+) ALL o A TKI in combination with FLAG-based chemotherapy	Clofarabine has not been considered as a comparator in this submission. • Clofarabine is licenced in R/R B-cell ALL for patients up to the age of 21, and only for patients receiving second treatment following relapse or failure to respond to induction therapy (that is, “second salvage”). As this appraisal is for the adult population, clofarabine represents an off-label comparator and is thus not deemed appropriate to compare to inotuzumab within this submission. • Additionally, consulted UK clinical experts estimate that in the UK adult population, clofarabine is used off-label in 10–15% of 18–30 year olds. In the UK adult population, under-30s constitute less than 30% of the expected eligible population; as such, clofarabine usage will be less than 5% of the total population in this appraisal. Therefore, it is too rarely used to be considered the standard of care for UK patients. TKIs in combination with FLAG-based chemotherapy, but not alone, for Ph+ patients.

			• TKIs are commonly used alongside chemotherapy-based regimens in Ph+ patients in UK clinical practice, however there is unlikely the use of TKIs *alone* in the R/R B-cell ALL population would occur. TKIs are hence included in addition to FLAG-based chemotherapy for Ph+ patients in the economic evaluation, but not alone. Best supportive care is not considered a relevant comparator. • Treatment with inotuzumab acts as a bridge to reaching potentially curative therapy. Therefore, a comparison to best-supportive care or palliative care is not considered appropriate.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Treatment response rates (including haematologic responses) • Time to and duration of response • Adverse effects of treatment • Health-related quality of life	Outcomes are reported to match the NICE scope. In addition, key outcomes of interest also include: • Minimal residual disease negativity (MRD-) • Rate of potentially curative therapy, such as HSCT	Not applicable
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The economic analysis was performed to meet the requirements of the NICE reference case.	Not applicable

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	None	None	Not applicable
Special considerations including issues related to equity or equality	None	None	Not applicable
Key: ALL, acute lymphoblastic leukaemia; FLAG, fludarabine plus cytarabine plus granulocyte-colony stimulating factor; HSCT, haematopoietic stem cell transplant; IDA, idarubicin; NHS, national health service.			

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Inotuzumab ozogamicin
Marketing authorisation/CE mark status	On 7th June 2013, orphan designation was granted by the European Commission. Inotuzumab is currently awaiting marketing authorisation, [redacted]
Indications and any restriction(s) as described in the summary of product characteristics	The expected indication is [redacted] orphan designation was granted by the EMA [redacted]
Method of administration and dosage	Inotuzumab is given intravenously, by infusion over 1-hour, at a starting dose of 1.8mg/m^2 (0.8mg/m^2 on Day 1 and 0.5mg/m^2 on Days 8 and 15). Cycle 1 lasts for 21 days but may be extended to 28 days if the patient achieves CR/CRi and/or to allow recovery from toxicity. Each subsequent cycle lasts for 28 days. Once a patient reaches CR/CRi, the starting dose on Day 1 of the cycle is reduced to 0.5mg/m^2 for the duration of treatment. Information on administration and dosing is taken from the draft SPC: For patients proceeding to HSCT, [redacted][1]
Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; EMA, European Medicines Association; HSCT, haematopoietic stem cell transplant; MRD, Minimal residual disease; VOD, veno-occlusive liver disease.	

1.3 Summary of the clinical effectiveness analysis

The use of inotuzumab for the treatment of R/R B-cell ALL is supported by the pivotal Phase III randomised controlled trial (RCT), INO-VATE 1022. This trial is summarised below:

- Phase III, global, multicentre (including eight sites in the UK), randomised, open-label, two arm study that enrolled adult patients (aged ≥18) with R/R CD22-positive ALL due to receive either first or second salvage therapy (i.e., first or second treatment following relapse or failure to respond to induction therapy [refractory disease]), and for whom either arm of randomised study therapy offered a reasonable treatment option.

- Both Ph- and Ph+ R/R B-cell ALL patients were included in the study, in line with the decision problem and [redacted].
  - Ph+ were also required to have failed treatment with at least one second- or third-generation tyrosine kinase inhibitor (TKI) and standard multi-agent induction therapy (which is in line with standard clinical practice in the NHS in England and Wales).
- Patients were randomised in a 1:1 ratio to receive either inotuzumab 1.8mg/m^2 per cycle (in a fractionated schedule of 0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15) (N = 162) or an investigators' choice of one of three standard of care chemotherapy regimens:
  - Fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) (n = 102)
  - Cytarabine plus mitoxantrone (CM) (n = 38)
  - High dose cytarabine (HIDAC) (n = 22)
- The INO-VATE 1022 trial presented head-to-head comparative efficacy versus the standard of care comparator in UK clinical practice, FLAG-based chemotherapy.

Achieving remission is typically a pre-requisite for potentially curative subsequent therapy. Inotuzumab demonstrates statistically significant improvements in the proportion of patients achieving complete remission (CR) or CR with incomplete haematological recovery (CRi) compared with standard of care (SoC) (see Section 4.7)

Achieving remission (CR or CRi) is typically a pre-requisite for potentially subsequent curative therapy, such as haematopoietic stem cell transplantation (HSCT), which is considered the main goal after salvage treatment.[2] In INO-VATE 1022, the CR/CRi rate was thus the primary endpoint, as assessed by the Endpoint Adjudication Committee (EAC) in the ITT218 population (the first 218 randomised patients).

In the inotuzumab arm, 80.7% (95% CI: 72.1–87.7) of patients achieved CR/CRi compared to only 29.4% (95% CI: 21.0–38.8) in the control arm. The rate difference was 51.4 (97.5% CI: 38.4, 64.3) and was statistically significant (p<0.0001). The results were consistent separately for both CR: 35.8% (95% CI: 26.8, 45.5) compared to 17.4% (95% CI: 10.8, 25.9), respectively (rate difference = 18.3% [97.5% CI: 5.2, 31.5; p=0.002]), and CRi: 45.0% (95% CI: 35.4, 54.8) compared to 11.9% (95% CI: 6.5, 19.5), respectively (rate difference = 33.0% [97.5% CI: 20.3, 45.8; p<0.0001]).

Results were consistent and also statistically significant in the total intent-to-treat (ITT) population, with a CR/CRi rate of [redacted]% (95% CI: [redacted]–[redacted]) compared to [redacted]% ([redacted]% CI[redacted], respectively (rate difference = [redacted]).

A statistically significantly higher number of patients treated with inotuzumab ([redacted]%) compared with SoC ([redacted]%) proceeded to potentially curative haematopoietic stem cell transplantation (HSCT) (see Section 4.7)

In the ITT population, [redacted]% of patients in the inotuzumab arm and [redacted]% of patients in the control arm proceeded to HSCT after study treatment (p<0.0001). Patients were included in this analysis after receiving study therapy but prior to the start of any post induction therapy (e.g. without another intervening induction therapy and regardless of CR/CRi status). Inotuzumab patients who achieved CR/CRi and received HSCT had a much higher 2-year survival probability compared to patients who did not receive HSCT [redacted]

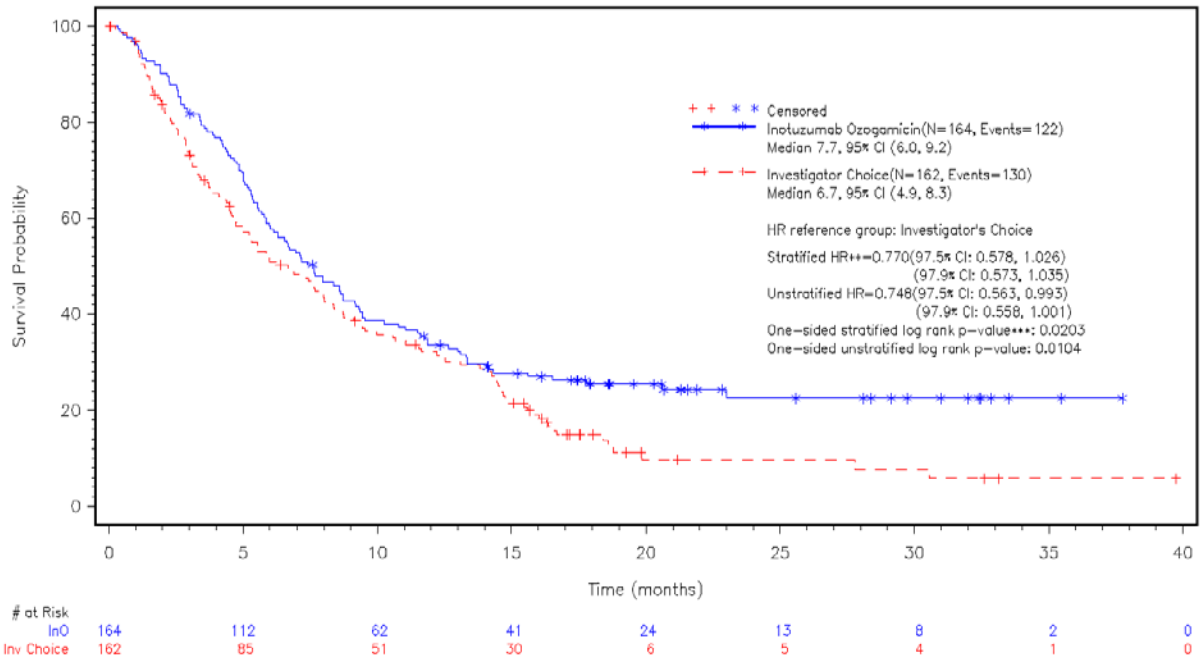
Although the main survival benefit of treatment with inotuzumab is demonstrated through getting more patients to HSCT, there remains a survival benefit for patients receiving inotuzumab who are not able to receive this (e.g., because they are unable to find a suitable donor). With or without censoring for HSCT, the probability of survival at 24-months is higher in patients treated with inotuzumab than the control arm (22.9% vs 9.6% without censoring for HSCT compared with [redacted] with censoring for HSCT, respectively).

Inotuzumab is associated with extended overall survival (OS) compared with SoC for patients who are otherwise at the end of life (see Section 4.7). The restricted mean survival benefit associated with inotuzumab is 3.9 months (13.9 months, SE: 1.10, vs. 9.9 months, SE: 0.85), as of last follow-up at March 2016 (data cut-off of 37.7 months).

In INO-VATE 1022, the stratified analysis of OS was associated with a hazard ratio (HR) of 0.77 (97.5% CI: 0.58, 1.03; p=0.0203) in favour of inotuzumab. The median OS was 7.7 months (95% CI: 6.0–9.2) in the inotuzumab arm compared to 6.7 months (95% CI: 4.9–8.3) in the control arm. It is worth noting that although this median result did not meet the pre-specified p-value,[redacted] a 1-sided test (0.025) for OS should be considered. This renders the improvement in OS associated with inotuzumab over control to be statistically significant. Most importantly, however, is the fact that the benefit of inotuzumab is seen in the Kaplan–Meier plot after the median survival point (Figure 1), with a possible plateau in survival becoming apparent with inotuzumab. At 6 months, the survival probability was [redacted]% (95% CI: [redacted]) in the inotuzumab arm compared to [redacted]% (95% CI: [redacted]) in the control arm; by 24 months, a far greater difference between the arms is present, at [redacted]% (95% CI: [redacted]) in the

inotuzumab arm compared to [redacted]% (95% CI: [redacted]) in the control arm. The benefit seen in the tail of the inotuzumab curve reflects, in part, the greater proportion of patients reaching HSCT and benefiting from this potentially curative therapy.

Figure 1: Kaplan–Meier plot of overall survival (ITT population)



Source: INO-VATE CSR[3]

What is also clear from the plot is that the difference in survival between the two arms varied according to the time from randomisation, and therefore, proportional hazards are not observed for these data. “Restricted mean survival time” (RMST) is an alternative approach often used to estimate the treatment effect, especially when the assumption of proportional hazards is not satisfied.[4-6] RMST has been presented and used within analysis of comparative clinical benefit in several recent NICE oncology appraisals where the proportional hazards assumption did not hold and the shape of the OS Kaplan–Meier plots in these instances are similar to those for inotuzumab.[7-10] In the ITT population, inotuzumab was associated with an RMST for OS of 13.9 months (SE: 1.10) compared to 9.9 months (SE: 0.85) in the control arm. This is a benefit in RMST of 3.9 months (95% CI: 1.21-6.65) in 37.7-month life expectancy, with a 1-sided p-value of 0.0023.

Inotuzumab meets the criteria for NICE to consider it a life-extending, end of life treatment. Current life expectancy is 6.7 months median, and 9.9 months restricted mean. Treatment with inotuzumab is associated with a restricted mean increase in OS of 3.9 months.

Life expectancy is short for adults with R/R B-cell ALL, with a median OS as low as 3 months with current therapies (as reported in the literature).[11-13] In the INO-VATE 1022 trial, median OS was 6.7 months with the standard of care, improved by 1.0 months with inotuzumab. However, the more statistically appropriate analysis of survival in this case is the RMST analysis (see Section 4.4). The RMST showed the standard of care was associated with a restricted mean survival time of 9.9 months, improved by 3.9 months with inotuzumab to 13.9 months, when restricted to a 37.7-month maximum follow-up (see section 4.7).

Although an appropriate measure of benefit and more relevant than the median, the RMST is, by definition, a restricted version of the true extrapolated mean. The mean extrapolated OS benefit associated with inotuzumab above standard of care (persisting past the RMST cut-off of 37.7 months) is modelled in excess of 5.6 months gain with inotuzumab (see Section 5).

For a more in-depth discussion on the end-of-life criteria, please see Section 4.13.

Treatment with inotuzumab is associated with statistically significant improvements in the proportion of patients achieving minimal residual disease (MRD)-negativity compared with SoC, which in turn is associated with improvements in OS (see Section 4.7)

Published studies have demonstrated that MRD-negativity is an important prognostic indicator for ALL correlating with improved long-term outcomes[14], and UK clinical expert feedback has also confirmed this. In the INO-VATE 1022 trial, patients who achieve MRD-negativity had longer survival times, and more patients treated with inotuzumab achieved MRD negativity.

Among patients who achieved CR/CRi, [redacted]% achieved MRD-negativity in the inotuzumab arm and [redacted]% in the control arm ([redacted]). For patients who achieved CR and CRi, these proportions were [redacted]% compared with [redacted]%, respectively (p<0.0001) and [redacted]% compared with [redacted]%, respectively (p=[redacted]).

Overall survival (median) for patients who achieved MRD-negativity was much [redacted] compared with those who did not: [redacted] months (95% CI: [redacted]) for inotuzumab arm and [redacted] (95% CI: [redacted]) months in the control arm, compared with [redacted] months (for both arms; 95% CI for inotuzumab: [redacted]; 95% CI for SoC: [redacted]) for those who did not; however, the proportion of patients who achieved MRD-negativity in the control arm compared with the inotuzumab arm was much smaller ([redacted] patients, respectively).

Inotuzumab demonstrates statistically significant improvements in progression-free survival (PFS) compared with SoC, indicating improved duration of remission (see Section 4.7)

The median PFS was 5.0 months (95% CI: 3.7–5.6) in the inotuzumab arm versus 1.8 months (95% CI: 1.5–2.2) in the control arm. The estimated HR (based on the stratified analysis) was 0.45 (97.5% CI: 0.34, 0.61; p<0.0001) in favour of inotuzumab.

When considering data from the INO-VATE 1022 trial, PFS is a more appropriate indicator of patients' duration of remission (DoR) than the actual DoR outcome. This is because at the time patients were identified as eligible for HSCT, no further bone marrow samples were collected, effectively censoring them from the study, and thereby shortening their reported DoR. This would result in patients who are still in CR/CRi and progressing to potentially curative HSCT (and therefore expected to have much longer duration of remission) being removed from the DoR analysis. Detailed DoR results are presented in Section 4.7.

Treatment with inotuzumab demonstrates improvements in health-related quality of life (HRQL) compared with SoC (see Section 4.7)

Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), quality of life (QoL), functioning, and symptoms were generally in favour of patients in the inotuzumab arm compared to patients in the control arm. Patients receiving inotuzumab were observed to have significantly better appetite, be significantly more ambulatory, and experience significantly less impact on family and social life across scales such as physical, role, and social functioning (estimated mean treatment difference >5 points, p<0.05). They were also observed to be significantly more able to perform strenuous activities, basic living needs, work, other daily activities, hobbies and other leisure activities. It is generally accepted that changes in HRQL scores between 5% and 10% are regarded by patients as being significant.[15] Global health status/QoL, dyspnoea, and fatigue reached or were close to clinical significance (estimated mean difference ≥5 points). There was no dimension that was clinically significantly worse for the inotuzumab arm compared to the control arm.

Using the EQ-5D, no clinically significant differences were observed between treatments, although EQ-VAS directionally favours the inotuzumab arm: this trend is consistent with the EORTC QLQ-C30 Global health status/QoL scale.

Inotuzumab is a targeted therapy that can be used for both Ph- and Ph+ patients, showing improvements in outcomes compared with SoC for both subgroups of patients (see Section 2.2 and Section 4.7)

Inotuzumab is expected to receive a license for use in R/R B-cell ALL patients with both Ph- and Ph+ subtypes. In the INO-VATE 1022 trial, inotuzumab demonstrated improvements in CR/CRi rates and OS compared to the control arm in both subgroups. Results for the Ph+ subgroup did not reach statistical significance because the study was not powered to reach significance within each subgroup, although the results for CR/CRi rates were approaching significance (p=0.08). It is, of course, mindful to be important to be mindful of the small number of Ph+ patients in the trial (which reflects the small proportion of patients with Ph+ disease in clinical practice, in an already rare disease) when seeking to draw conclusions with respect to the statistical significance of these data.

Inotuzumab demonstrated a more favourable toxicity profile than the chemotherapy-based SoC treatments used in the control arm (see Section 4.12)

Inotuzumab patients received a median of 3.0 cycles of therapy (range: 1.0, 6.0) compared to only 1.0 cycles (range: 1.0, 4.0) for patients in the control group; therefore, it is more appropriate to compare overall treatment-emergent adverse event (TEAE) rates only for the first cycle of treatment. It should be noted that TEAE for subsequent treatments received by the SoC arm was not collected, even though these subsequent treatments contributed to the OS result in that arm. As such, a comparison of all cycle TEAE may be biased in the favour of SoC.

During Cycle 1 only, [redacted] ([redacted]%) patients in the inotuzumab arm and [redacted] ([redacted]%) patients in the control arm reported TEAEs; [redacted] ([redacted] %) patients compared to [redacted] %) patients, respectively, reported severe adverse events (SAEs), and [redacted] ([redacted] %) patients compared to [redacted] ([redacted] %) patients, respectively, reported Grade 3 or 4 TEAEs. The TEAEs that occurred most frequently in the inotuzumab arm generally occurred less frequently than those seen in the control arm (except for neutropenia, fatigue, alanine transaminase elevation, gamma-glutamyl transpeptidase elevation, and hyperbilirubinaemia when considered across all cycles). During Cycle 1 only, there were no TEAEs that occurred more frequently in the inotuzumab group than in the control group. Even across all treatment cycles (noting the average treatment duration was lower in the control arm), there were still many more TEAEs that occurred with a higher frequency in the control group than in the inotuzumab group.

The most common (≥20% in either arm) all-cause Grade ≥3 TEAEs were neutropenia, thrombocytopenia, febrile neutropenia, leukopenia, anaemia and lymphopenia. All of these most frequently occurring Grade ≥3 TEAEs occurred in a much larger proportion of patients in the control group, with the exception of

neutropenia, which occurred in slightly more patients in the inotuzumab group ([redacted]%). However, concern over the gravity of neutropenia is typically only if it begins to impair quality of life for patients, such as the development of febrile neutropenia, which occurred far more frequently for control patients ([redacted]%). Bacteraemia also occurred more commonly for control patients ([redacted]%).

The pre-specified SAE, veno-occlusive disease (VOD), was more commonly experienced in the inotuzumab arm than in the control arm ([redacted]% patients, respectively [p<0.001]). VOD is a known complication of HSCT, occurring in 10–15% of patients following allogeneic HSCT conditioned with a myeloablative regimen.[16] The occurrence of VOD within the trial is higher than would be expected in UK clinical practice, but is attributable to different treatment approaches and experience with HSCT among the countries and institutions included in the trial. Countries and institutions with more experience managing VOD, such as the UK and the US, experienced the lowest incidence rates, which were similar to those for chemotherapy patients. In addition, in multivariate analysis, patients who had received dual alkylator conditioning (which is not commonly used in the UK) for HSCT (OR = [redacted]) and older patients (≥55; OR = [redacted]) were more likely to experience VOD. Higher rates of VOD also occurred in patients who had received a prior HSCT, and the rate is much lower when patients without prior HSCT were viewed separately.[17] Patients are not eligible for a second HSCT under the current NHS England funding structure, and therefore, rates of VOD would be expected to be much lower in clinical practice.

1.4 Summary of the cost-effectiveness analysis

The modelled patient population reflects UK patients with R/R B-cell ALL, and the comparator in the base case is representative of therapy currently used in UK clinical practice (see Section 5.2.3).

The cost-effectiveness analysis considered patients with R/R B-cell ALL. This is consistent with the decision problem as outlined in Table 1, with the anticipated licensed indication for inotuzumab, and with the available head-to-head clinical trial evidence for both Ph+ or Ph– patients.

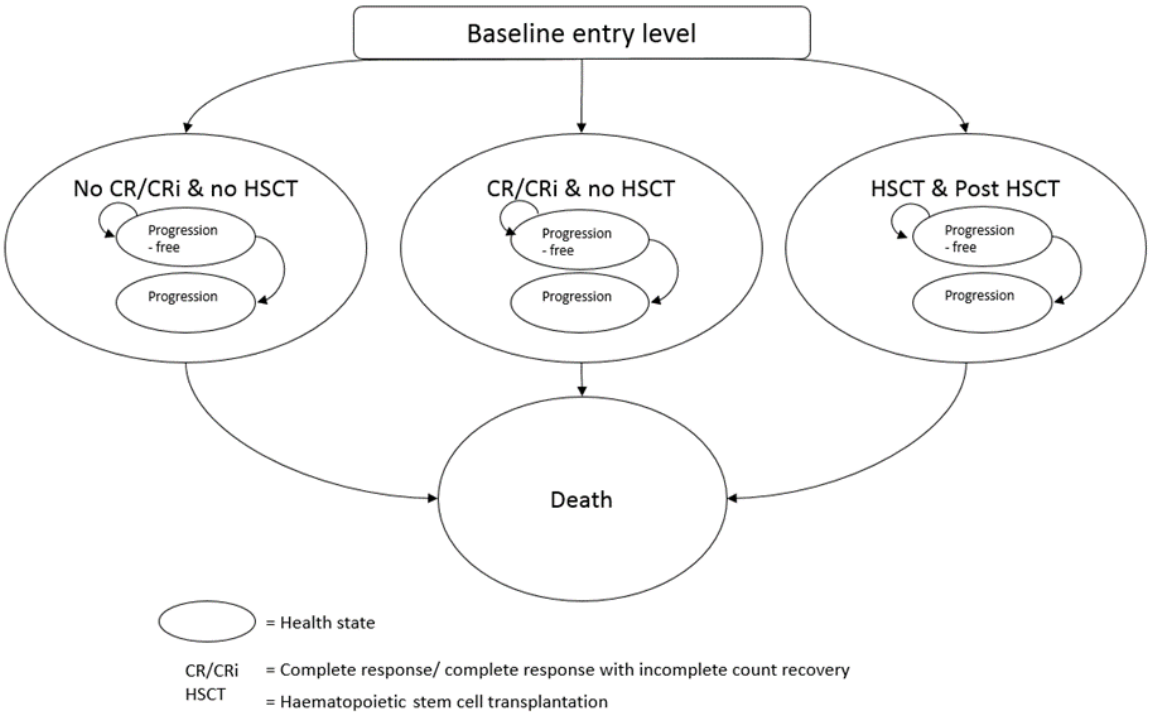
The primary comparator for inotuzumab within the cost-effectiveness analysis was “standard of care”, which is a treatment mix of FLAG/FLAG IDA, HIDAC and CM, as per the INO-VATE 1022 trial, with each comparator also evaluated independently in scenario analyses. Imatinib was included in the model as the representative TKI for Ph+ patients. Feedback from UK clinical experts indicated that FLAG/FLAG IDA would most commonly be used in a UK setting and that the efficacy of these treatments observed in the trial were reflective of those administered in UK clinical practice in the treatment of R/R B-cell ALL.

The model design reflects the disease pathway and was validated through consultation with treating UK clinical experts. The design is consistent with the NICE reference case (see Section 5.2.2).

The main goal of any treatment for ALL within the UK is to reach subsequent (potentially curative) HSCT, for which remission is typically a pre-requisite. The cost-effectiveness analysis therefore used a model that partitions patients based upon their level of remission (CR/CRi), and then whether they went on to receive subsequent potentially curative therapy (HSCT) in the model.

After treatment (with either the intervention or comparator) in the '*Baseline Entry Level'* state, the model partitions patients to one of four health states, each defined by a combination of their response to treatment and subsequent receipt (or not) of HSCT: '*No CR/CRi & no HSCT', 'CR/CRi & no HSCT', 'HSCT & Post-HSCT'* (which incorporated patients both *CR/CRi* and *No CR/CRi)* and '*death*' (Figure 2). PFS was modelled within each of these states (excluding death), as disease progression can occur at any time. From within these partitions, an 'area under the curve' structure was used in a deterministic framework to determine patients' survival. This design, which differs from the three-state Markov structure typical of oncology models, was used because patients' survival is largely influenced by the extent to which they achieve remission, particularly for patients who are ineligible for HSCT (see Section 5.3). In addition, there is evidence to suggest that a patients' quality of life will differ depending upon whether they achieve remission and whether they undergo HSCT.[18] It is therefore appropriate to model the level of remission and HSCT as different health states.

Figure 2: Model structure diagram



Note: Patients can receive HSCT whether they are No CR/CRi or CR/CRi.

The analysis was conducted in line with Reference Case from the perspective of the NHS and the Personal Social Services (PSS) in England and Wales. The analysis was run using 28-day model cycles, in line with treatment regimens, with a time horizon of 60 years (reflecting the maximum life expectancy of patients, thereby accounting for the impact of potentially curative subsequent therapy).

Discount rates of 3.5% and 1.5% were used for the base case. As discussed, the key goal of treating R/R B-cell ALL (with inotuzumab or SoC) is to bridge to potentially curative therapy, with much of inotuzumab's benefit stemming from its ability to get more patients to HSCT. In such instances when treatment costs are incurred upfront, but benefit extends into the very long term, discounting disproportionally effects the benefits (i.e., decreases QALYs) relative to its effect on the immediately-incurred costs. To minimise the differential impact of discounting on costs and benefits, the NICE Methods Guide states that in such cases when treatment restores people who would otherwise die to near full health over a very long period, a lower discount rate of 1.5% may be considered. Results with both discount rates (1.5% and 3.5%) are therefore presented for inotuzumab.

The INO-VATE 1022 Phase III trial provided direct head-to-head evidence for inotuzumab versus the standard of care; this trial provided both clinical input and on-treatment utility data used in the model. UK costs were used in line with NICE recommendations (see Section 5.4).

Clinical data incorporated into the model were based on the Phase III INO-VATE 1022 data, with parametric curve fitting used to extrapolate outcomes beyond the trial follow-up period (see Section 5.3). These data were specific to each health state, which reflects the different probabilities of time-dependant survival related to each state. Following UK clinical expert feedback which recommended explicit consideration of patient outcomes with respect to the presence of specific attributes that would increase their eligibility for HSCT, these characteristics were included in covariate-adjusted PFS and OS analysis. The covariates considered within the analysis were regarded by clinicians as important prognostic factors of a patient's outcome, and included Ph status, age, duration of remission, geographical region, and whether the patient had undergone a prior HSCT.

Utilities for the states defined by no subsequent HSCT ('*No CR/CRI & no HSCT*' and '*CR/CRi & no HSCT'*) were derived from the EQ-5D data captured directly from within the INO-VATE 1022 trial. To avoid double-counting, disutilities for adverse events (AEs) already captured within the EQ-5D data were not included; however, disutilities were included for AEs that occur outside of the timeframe of the EQ-5D data capture. This included disutilities for graft versus host disease (GvHD), VOD, and the AEs associated with HSCT. Utility data for post-progression and post-HSCT were not available from the trial, so were obtained via a review of the available literature, including prior HTA appraisals. Utility data for the patients post-HSCT was time dependent, reflective of the time since transplantation. All utilities obtained from sources outside the INO-VATE 1022 trial were verified by UK clinical experts as appropriate in the absence of relevant data from within the trial.

Costs were applied to the model from the perspective of the NHS and PSS, including drug acquisition costs, administration costs (where relevant), subsequent treatment costs, and the costs of managing AEs (see Section 0). Key points of differentiation between the two arms were captured in the model, such as the administration costs. The UK current SoC (FLAG) is commonly administered over a five-day period in an inpatient setting; by contrast, inotuzumab can be administered in an outpatient setting. In addition to the impact of patient-reported quality of life, the more convenient administration of inotuzumab brings with it significant healthcare resource use reductions.

The costs of HSCT and follow-up costs associated with HSCT were included in the model. In addition, a single cost for terminal care was applied (see Section 5.5.6.2). Any monitoring costs that were not treatment-specific would necessarily apply to both arms equally, and therefore were not included (as they result in no incremental difference between the arms). All given unit costs were derived from the latest NHS

reference costs (2015–16), and where unit costs were not available prices were inflated using the PSSRU inflation indices.

The incremental cost-effectiveness of inotuzumab versus standard of care chemotherapy for the treatment of R/R ALL ranged from £40,013 to £55,869 per QALY, dependent on the discount rate used (see Section 5.7). When the cost-effectiveness calculations are adjusted so as to not disadvantage the longer-term survival benefits offered by inotuzumab, it clearly represents a cost-effective use of NHS resources treatment in an orphan population with an end-of-life disease.

The deterministic incremental cost-effectiveness ratio (ICER) ranged from £40,013 to £55,869 per QALY, dependent on using a 1.5% or 3.5% discount rate for costs and benefits, respectively. The mean probabilistic ICERs were comparable to the deterministic, however ranged higher (between £48,000 and £67,000 per QALY), when the uncertainty of post-HSCT OS was also included. However, uncertainty around longer term survival is likely related not to inotuzumab, but to the efficacy of HSCT, for which the benefits have already been explored within the literature and prior appraisals. Therefore, this uncertainty within the model does not necessarily extend to uncertainty in real practice.

The results of the base case analysis for inotuzumab are presented in Table 3.

Table 3: Deterministic base case results

	Incremental			ICER (inotuzumab vs SoC)
	Costs	**QALYs**	**LYs**	
Costs and benefits discounted at **1.5%**	£[redacted]	[redacted]	5.18	£40,013
Costs and benefits discounted at **3.5%**	£[redacted]	[redacted]	5.18	£55,869

Key: ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.

Modelled estimates of extrapolated mean OS predict a survival advantage with inotuzumab versus standard of care greater than 5.2 years (see Section 5.3). This is reflective of the higher proportion of patients achieving a bridge to curative therapy and experiencing normal population life expectancy.

The cost-effectiveness evaluation estimated that patients receiving inotuzumab experience a mean increase in survival of 5.18 years (undiscounted), and a mean of [redacted] additional QALYs (discounted at 1.5%) compared with the standard of care. Expert UK clinicians consulted on the increase in means OS with inotuzumab explained that this benefit is a driven by the increased remission rates and increased

MRD negativity observed in the inotuzumab arm of the INO-VATE 1022 trial, which results in an increased proportion of patients are able to reach HSCT. Once patients remain alive past 3 years in the model their life expectancy reverts to that of the normal population. This assumption is within the range of with previous literature, appraisals, and clinical expert opinion, and enforces the importance of considering the benefit in the tail of the Kaplan–Meier curve. This 'cure point' was varied in scenario analyses and found to not substantially impact the results.

The modelled OS estimates support the consideration of inotuzumab as an end-of-life medicine (detailed in Section 4.13) with both the standard of care being less than a mean of 2 years and the intervention increasing life expectancy by greater than 3 months. As a treatment for an orphan condition, inotuzumab necessarily meets the third criterion regarding patient population size.

Key scenario analyses applicable to the UK setting demonstrate that inotuzumab is consistently associated with cost-effective ICERs versus standard of care chemotherapy, and indeed illustrate that the base case ICER may be a conservative estimation of the value for money inotuzumab can offer to patients in the NHS.

Scenario analyses were conducted to reflect possible nuances in UK clinical practice. Although clinical experts confirmed the trial results would be generalisable to patients within the UK, the following scenarios may be of particular relevance for decision making:

1. Limiting inotuzumab treatment to 3 cycles only (in line with the draft UK SPC)
2. Exploring the SCT covariate within the model to determine the cost-effectiveness when only patients with no prior SCT are considered (reflecting that for many patients in the UK, funding for only one HSCT is available)
3. Exploring the cost-effectiveness of only treating patients with FLAG within the SoC arm (n=102 from 162). FLAG is the specific chemotherapy regimen specified in the scope.
4. Use of utility inputs that have been accepted for a UK population: adjustment of utility to match that accepted in a recent appraisal for use in NHS Scotland.

All four of these key scenarios reduced the base case deterministic ICER range down to between £34,311 to £39,027 per QALY using discount rates of 1.5%. The probabilistic ICER range was reduced to between £41,610 and £47,120 per QALY. These scenarios suggest the base case ICERs present conservative estimate of inotuzumab's cost-effectiveness within the NHS.

Further exploratory sensitivity analyses supported the robustness of the base case results, and show that the cost-effectiveness of inotuzumab is consistent and robust across plausible clinical scenarios versus standard of care chemotherapy (see Sections 5.7).

One-way sensitivity analyses indicated that the key drivers of the model were in utility values (notable utilities associated with progressive disease and HSCT) and costs associated with HSCT. Additional key drivers were in relation to the parameters surrounding veno-occlusive disease (VOD) and the proportion of patients receiving specific subsequent treatments (see Section 5.8). Given the costs associated with HSCT, VOD and blinatumomab, these parameters are not unexpected. However, it should be noted that the cost of HSCT and subsequent therapies are independent of inotuzumab, and these costs will continue to be the drivers of cost-effectiveness in the disease area, regardless whether the intervention or standard of care is used.

Similarly, as the benefit of inotuzumab is that it allows more patients to receive HSCT and therefore patients receive a curative therapy and survive longer, it is not surprising that long-term utilities associated with progressed disease and long-term outcomes are key drivers of the model.

Inotuzumab is targeted at a small patient population; the budget impact of the introduction of inotuzumab into the R/R B-cell ALL setting is estimated to be £[redacted] over 5 years.

On the introduction of inotuzumab, the net budget impact on the NHS in England and Wales is estimated at £[redacted] (see Section 6). This includes the drug acquisition costs, the treatment administration costs, and all costs considered within the model (subsequent therapy, HSCT, and AE management). Given an anticipated patient population of 117 in 2017, the analysis assumes a market share uptake of [redacted]% to [redacted]% over a 5-year period (see Section 6 for more details).

Concluding remarks

Inotuzumab for the treatment of adult patients with R/R B-cell ALL, is a valuable treatment option for patients in England and Wales and represents value for money to the NHS for the following reasons:

- R/R B-cell ALL is a rare condition, with limited evidence available for treatments in this population and limited guidelines around treatment options for patients.
- Life expectancy for R/R B-cell ALL patients is poor with the current SoC, with median survival as low as 3-months.
- Therefore, there remains an unmet need for this patient population.
- Direct head-to-head, RCT evidence demonstrates that inotuzumab is efficacious for the treatment of R/R B-cell ALL and results in improvements in the proportion of patients achieving CR/CRi; the proportion of patients going on to receive potentially curative HSCT; progression-free survival; overall survival, improvements in the proportions of patients achieving MRD negativity and in HRQL outcomes, compared to SoC chemotherapy treatments.
- Inotuzumab meets the end of life criteria, as current life expectancy is estimated between 3 and 9.9 months with SoC treatments (see Section 3.4) to which inotuzumab offers a restricted mean extension of 3.9 months (see Section 4.7). Inotuzumab will also be used to treat a very small patient population.
- Inotuzumab is well tolerated, with a more favourable toxicity profile than the chemotherapy-based SoC treatments and adverse events could be managed within existing NHS framework (see Section 4.12).
- Inotuzumab offers a convenient administration schedule, with no requirement for hospitalisation to receive treatment, and with reduced hospitalisations for management of disease and adverse events due to its improved superior efficacy and safety profile
- The incremental cost-effectiveness of inotuzumab is versus standard of care chemotherapy for the treatment of R/R ALL ranged from £40,013 to £55,869 per QALY for the 1.5% and 3.5% discount rates respectively (see Section 5.7)
- The modelled clinical outcomes were validated against clinical outcomes from the evidence base. The model supports a survival advantage associated with inotuzumab as a result of the treatment acting as a better bridge to potentially curative therapy than the standard of care
- Key scenario analyses applicable to the UK setting demonstrate that inotuzumab is consistently associated with cost-effective ICERs versus standard of care chemotherapy, and indeed illustrate that the base case ICER may be a conservative estimation of the value for money inotuzumab can offer to patients in the NHS (see Section 5.8.3)
- The budget impact of inotuzumab to the NHS in England and Wales, inotuzumab is estimated to be at [redacted] in Year 1 increasing to [redacted] in Year 5 (see Section 6)

2. The technology

2.1 Description of the technology

Brand name: Besponsa®

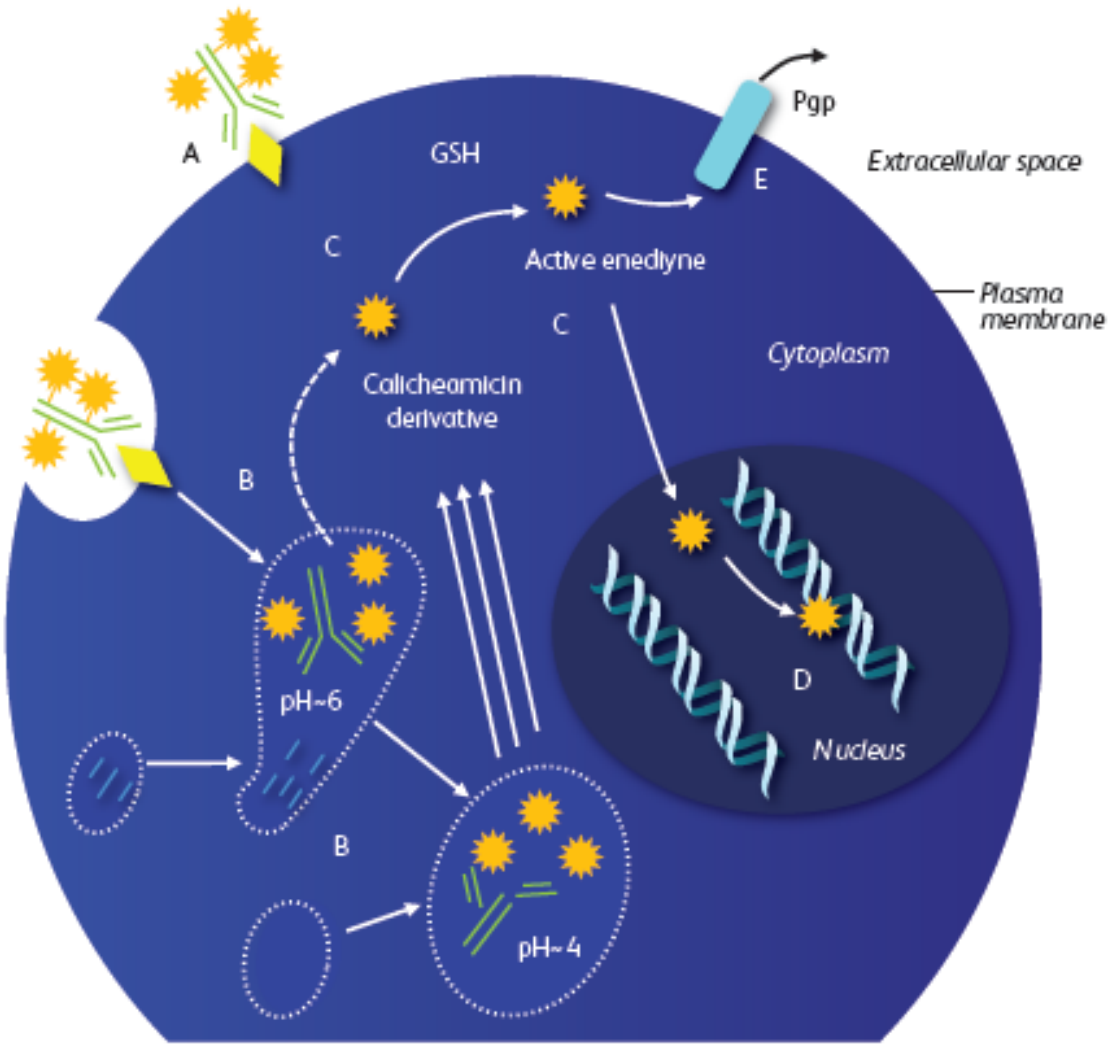
UK-approved name: Inotuzumab ozogamicin

Therapeutic class: Anti-CD22 antibody drug conjugate

Mechanism of action: Inotuzumab ozogamicin (inotuzumab) utilises a novel, targeted mode of action to limit systemic toxicity in the destruction of cancer cells, which means that it is well-tolerated and has a more manageable and ultimately less resource-intensive safety profile compared to other chemotherapy agents.

Inotuzumab ozogamicin (Inotuzumab is an antibody-drug conjugate (ADC) that consists of a derivative of calicheamicin (a cytotoxic antibody agent) attached to an engineered humanised monoclonal immunoglobulin G4 (IgG4) antibody, which targets CD22.[19-23] CD22 is expressed in up to 100% of mature B-cell acute lymphoblastic leukaemia (ALL) and in 93% to 96% of cases of B-cell precursor ALL. It is not expressed on haematopoietic stem cells or any other cells of haematopoietic or non-haematopoietic lineages, and it is not shed into the extracellular matrix and is therefore an attractive target for B-cell cancers.[24-33] After the conjugate binds to CD22 on the surface of the B-cells, the CD22-conjugate complex is rapidly internalised forming an endosome. Subsequently, the CD22 receptor-inotuzumab complex containing endosomes fuses with lysosomes, followed by intracellular release of calicheamicin. Calicheamicin binds to minor grooves of DNA in a sequence specific manner and thus induces the breakage of double-stranded DNA and results in subsequent cell death.[19, 21-23, 34-36] This process is presented in Figure 3.

Figure 3: Mechanism of action of inotuzumab



Key: ADC, antibody-drug conjugate; GSH, glutathione; Pgp, P-glycoprotein.
Notes: A, Inotuzumab binds to cell surface CD22 receptors and is rapidly internalised as a CD22 ADC complex.
B, ADC traffics from endosome to lysosome; the change in pH from 6.5–4.5 leads to progressive linker cleavage.
C, Calicheamicin derivative is released intracellularly and is activated by GSH.
D, Calicheamicin binds to the minor groove in DNA and causes double-strand cleavage, resulting in apoptosis (cell death).
E, Pgp-mediated drug efflux may be a resistance mechanism in leukaemia cells.
Source: de Vries et al. (2012)[37]

2.2 Marketing authorisation/CE marking and health technology assessment

Inotuzumab is a designated orphan drug in Europe[38] and the US[39] with an anticipated indication [redacted].[1]

Inotuzumab is currently awaiting marketing authorisation with the EMA, expected [redacted] with inotuzumab [redacted].It is anticipated that the license will be approved for the same population for which it was granted orphan designation by the EMA and for which pivotal trial evidence is available.

The current draft of the summary of product characteristics (SPC) to be submitted to the EMA is provided in Appendix 1. The only contraindication listed in this SPC is in patients with known hypersensitivity to inotuzumab or to any component of the product formulation.

Approval with the US Food and Drug Administration is anticipated in [redacted].

It is anticipated that Pfizer [redacted]

2.3 Administration and costs of the technology

Administration details and costs of inotuzumab are summarised in Table 4.

Based on the INO-VATE 1022 trial, inotuzumab is given intravenously at a starting fractionated dose of 1.8mg/m^2 per cycle (0.8mg/m^2 on Day 1 and 0.5mg/m^2 on Days 8 and 15). Cycle 1 lasts for 21 days, and each subsequent cycle last for 28 days. Once a patient reaches complete remission (CR), or complete remission with incomplete haematologic recovery (CRi), the dose on Day 1 of each cycle is reduced to 0.5mg/m^2 for the duration of treatment. More details on the number of vials of inotuzumab used per cycle and the estimated average cost per cycle (including how these were calculated) are presented within Section 5.

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Solution for infusion	Draft SPC
Acquisition cost (excluding VAT)[a]	[redacted] per vial	
Method of administration	Intravenous infusion	Draft SPC
Doses	Starting fractioned dose of 1.8mg/m^2 per cycle (0.8mg/m^2 on Day 1 and 0.5mg/m^2 on Days 8 and 15). Once a patient reaches CR or CRi, the starting dose on Day 1 of each cycle is reduced to 0.5mg/m^2	Draft SPC
Dosing frequency	Cycle 1 lasts for 21 days (but may be extended to 28 days if the patient achieves CR/CRi and/or to allow recovery from toxicity), with each subsequent cycle lasting for 28 days. Treatment within each cycle is given on Day 1, Day 8 and Day 15.	Draft SPC
Average length of a course of treatment	The draft SmPC (Appendix 1) states that for [redacted] The median number of cycles received in INO-VATE 1022 for inotuzumab patients was 3. [redacted] Over the course of treatment, it is estimated that an average of 9.49 vials will be administered (estimated from the method of moments, which includes wastage; see Section 5 for further details).	Draft SPC, INO-VATE 1022
Average cost of a course of treatment	[redacted]	
Anticipated average interval between courses of treatments	None	
Anticipated number of repeat courses of treatments	None	
Dose adjustments	Once a patient reaches CR or CRi, the starting dose on Day 1 of each cycle is reduced to 0.5mg/m^2 if	Draft SPC

	Cost	Source
	treatment is continued. Dose modification may be required based on individual safety and tolerability. Management of some adverse drug reactions may require dosing interruptions and/or reductions, or permanent discontinuation. If the dose is reduced due to drug-related toxicity, the dose should not be re-escalated.	
Anticipated care setting	Outpatient setting	Draft SPC

Key: CR, complete response; CRi, complete response with incomplete count recovery; SPC, summary of product characteristics.
Notes: [a]Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.4 Changes in service provision and management

No additional tests or investigations are needed for treatment eligibility outside of those required in clinical practice for patients with ALL.

Inotuzumab should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available. Patients should be observed during and for at least 1 hour after the infusion for symptoms of infusion-related reactions. Hospital oncology units already have the staffing and infrastructure needed for the administration of such cancer treatments. It is anticipated that the administration of inotuzumab would utilise this existing NHS infrastructure.

Unlike standard chemotherapy treatment, such as fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) (FLAG)-based chemotherapy, which requires patients to be admitted to the hospital and treated on an inpatient basis, inotuzumab can be administered in the outpatient setting, with patients treated as a day case. Therefore, there will be no hospital admissions related to administration as opposed to current 5 to 6 days with standard of care (see Table 64 for further details), which will result in reduced resource use for the NHS. As with current chemotherapy-based treatment, inotuzumab patients would be treated as needed for side effects of disease and treatment on an inpatient basis, and would make use of existing NHS infrastructure; inotuzumab has a more favourable efficacy and toxicity

profile in comparison to standard chemotherapy (Section 4.12) resulting in potential savings in the management of current disease and treatment-related adverse events (AEs).

For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤10,000/mm^3 is recommended prior to the first dose. Premedication with a corticosteroid, antipyretic and antihistamine is also recommended prior to dosing for all patients. There are no additional requirements for concomitant medications outside of what might usually be required for the usual treatment of relapsed or refractory (R/R) B-cell ALL.

The draft SPC recommends the following monitoring requirements for treatment with inotuzumab:

[redacted]

[redacted]

These monitoring requirements would usually be undertaken in standard practice within the NHS for all R/R B-cell ALL patients regardless of which treatment they

received, and therefore, inotuzumab would be expected to utilise this existing NHS infrastructure.

All resource requirements associated with inotuzumab treatment are fully accounted for in the economic modelling presented in Section 5.

2.5 Innovation

Overall, inotuzumab represents a step-change in disease management in a population for whom there is a poor prognosis, significant unmet need and limited treatment options (see Section 3 for more detail).

- Inotuzumab, through a novel mechanism of action, has demonstrated unprecedented rates of complete remission, which allows for significantly more patients to progress to potentially curative therapies. This is shown by significant improvements in the HSCT-rate (potentially curing a proportion of patients) compared to standard therapy.
- Inotuzumab also demonstrates significant improvements in minimal residual disease (MRD) negativity, and health-related quality of life (HRQL) outcomes, and a meaningful survival benefit versus chemotherapy.
- Inotuzumab utilises a novel, targeted mode of action to limit systemic toxicity in the destruction of cancer cells, which means that it is well-tolerated and has a manageable safety profile compared to other chemotherapy agents.
- Inotuzumab offers a convenient administration schedule, with no requirement for hospitalisation to receive treatment, and with reduced hospitalisations for management of disease and AEs due to its improved superior efficacy and safety profile.

Improved efficacy

B-cell ALL is a rare and frequently fatal leukaemia. It is commonly diagnosed in children and it therefore impacts patients at an early stage of life, which has a significantly wider societal burden than diseases found more frequently in older patients (noting this appraisal is for adults). There is a lack of clear guidance on treatment options for these patients, and with the currently available treatments, long-term disease-free survival after initial treatment is achieved only in a minority of

adult patients[40], with approximately 44% experiencing a relapse and an additional 4% being refractory to treatment[41], although the proportion experiencing relapse could be as high as 60–70%.[42] Adult patients account for a much higher proportion of ALL-related deaths than paediatric patients[43], and following relapse, overall survival (OS) is around 3 to 6 months for patients who do not receive further potentially curative therapy, such as HSCT. It is important to note that in UK standard practice, HSCT is only possible in patients with no active disease, meaning that with the limited success of current treatments, few patients are able to access these potentially curative therapies.[14] Therefore, due to the rarity of the disease, high relapse rates, poor survival outcomes and a lack of clear guidance on treatment options for these patients, there is a serious unmet need for adult patients with R/R B-cell ALL.

Given the demonstrable unmet need, inotuzumab represents an important treatment for R/R B-cell ALL. Inotuzumab is not only associated with much higher rates of CR/CRi than the current standard of care, but also with statistically significant PFS improvements and statistically significant and clinically meaningful improvement in MRD negativity. Published studies have demonstrated that MRD-negativity is an important prognostic indicator for ALL correlating with improved long-term survival outcomes.[44-46] Importantly, these results suggest that inotuzumab will allow many more patients to progress to potentially curative treatments, such as HSCT (See Section 4.7), than currently available treatments will. Inotuzumab's ability to get an increased number of patients to transplant has a significant impact on OS, and potential, long-term improvements in the patients HRQL (See Section 3.2).

Considering this ability to bridge patients, with an otherwise terminal and aggressive disease, to a cure, inotuzumab can prove an essential treatment option for the NHS.

Novel mode of action and improved safety profile

There are currently no targeted treatment options available for patients with R/R ALL and no targeted treatment options available for patients with Ph- B-cell ALL, with current options limited to chemotherapy, or palliative care for those patients unable to tolerate more active treatment. Chemotherapy treatments are also associated with high levels of toxicity.

Inotuzumab is an innovative ADC in B-cell ALL that exploits the selective presence of CD22 surface antigens on ALL cells to specifically target malignant cells.[21, 47] This innovative mechanism of action selectively delivers a cytotoxic agent to tumour cells, while minimising systemic toxicity and limiting harm to the bone marrow; the source of healthy replacement cells.[21] The Committee for Orphan Medicinal Products acknowledged that:

"…inotuzumab ozogamicin might be of significant benefit for the treatment of B-cell ALL because it selectively targets the abnormal B-cell causing the leukaemia and early studies show beneficial effects in patients not responding to previous treatment."[38]

Inotuzumab is associated with a reduced toxicity profile when compared to chemotherapy (see Section 4.12). In general, inotuzumab does not result in higher AE rates despite a higher median number of cycles.[3] Common AEs seen with chemotherapy such as infections, thrombocytopenia, anaemia, and febrile neutropenia were lower in patients receiving inotuzumab compared to investigator's choice of chemotherapy, despite the higher median number of treatment cycles for inotuzumab.[3]

Inotuzumab is licensed for use in both Ph- and Ph+ patients, and provides a safe and effective, targeted treatment option for all patients with R/R B-cell ALL.

Improved administration for patients over current therapy

Patients currently treated with chemotherapy (most commonly FLAG-based treatment in the UK[48]) are admitted to hospital for treatment as an inpatient, typically for 5 to 6 continuous days (see Table 64). In addition to this inconvenience to patients which will undoubtedly impair quality of life, chemotherapy treatments are associated with high levels of toxicity; patients are often treated for side effects such as febrile neutropenia, also as an inpatient.

Inotuzumab has advantages for patients over chemotherapy in these respects, including a convenient administration schedule with no requirement for hospitalisation (inotuzumab is administered in an outpatient setting). This convenient administration is considered advantageous for these patients particularly when considering their limited life expectancy (literature estimating median OS as little as 3 months[11-13]). As such, anything to minimise their level of hospitalisation is considered

a large benefit, reinforced by UK clinical experts at a recent advisory board.[48] Further, as discussed above, inotuzumab also has a more favourable safety profile with lower incidence of febrile neutropenia (see Section 4.12), expected to result in fewer and shortened hospital stays.[3] This is beneficial to patients, their caregivers, and to the health service.

3. Health condition and position of the technology in the treatment pathway

Summary of the health condition and treatment pathway

R/R B-cell ALL

- ALL is a rare disease. Although it represents the most common type of childhood cancer, adults account for only 40% of ALL cases but 80% of ALL deaths, suggesting a more aggressive course of the disease. This is a result of adults being more likely to be diagnosed with unfavourable cytogenetic abnormalities.
- ALL is stratified into T-cell ALL and B-cell ALL (accounting for 75% of ALL patients), which can be further broken down as Ph- and Ph+ patients.
- Approximately 44% of adult patients with B-cell ALL are expected to relapse, with a further 4% demonstrated to be treatment refractory (although the number of patients relapsing may be as high as 60–70%).

Effects of R/R B-cell ALL on patients and carers

- B-cell ALL often manifests as a variety of non-specific symptoms, including fatigue, fever, weight-loss, dyspnoea (difficulty breathing), dizziness, increased rate of infection, and augmented bruising or bleeding, as well as possible central nervous system involvement (~10%) and enlarged lymph nodes, liver and spleen (~20%).
- There is limited evidence to illustrate the HRQL burden in R/R B-cell ALL patients and their caregivers, but in general, patients experience poor HRQL with impairments in specific assessment domains including role, physical and social functioning.
- Current treatment options (i.e. chemotherapy-based regimens) are also associated with a high toxicity burden, which may negatively impact on patients' HRQL.
- The aim of treatment is for patients to achieve CR/CRi in order to be able to receive potentially curative therapies, such as HSCT.
- R/R B-cell ALL is also associated with considerable carer burden, which is related to symptom severity and adverse effects of current treatment options.

Expected patient numbers and current life expectancy

- Prognosis for R/R B-cell ALL is poor, with 5-year OS in these patients is estimated to be less than 10%. Median OS may be as low as 3 months with current salvage therapies, which have low rates of CR/CRi and, therefore, very few patients (5–30%) progressing to further potentially curative therapies, compared with over 14 months for patients receiving HSCT.
- OS for standard of care in the INO-VATE trial is reported as 6.7 months (although this may be confounded by subsequent therapies).
- Around 117 patients per year are expected to be eligible for inotuzumab in England and Wales.
- Inotuzumab is being submitted for consideration as an end-of-life medicine.

Treatment pathway and existing NICE guidelines

- R/R B-cell ALL is a rare disease, and therefore, there are currently no clinical guidelines from NICE relevant to this population in NHS England.
- Current treatment options are very limited and include chemotherapy-based regimens, of which FLAG-based regimens are most commonly used.
- Because of the rarity of the condition and lack of guidance, the patient pathway at this point is extremely heterogenous, and is based heavily upon decision-making at the individual patient level, emphasising the need for increased treatment options.

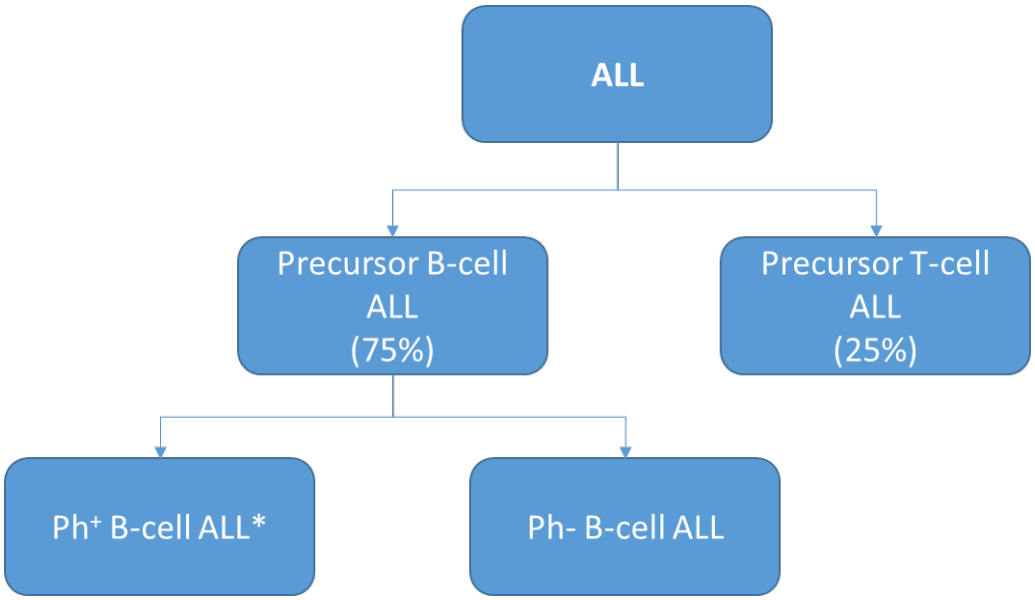
3.1 Disease overview

Leukaemia is a type of cancer that originates in the bone marrow, often disseminating into the blood and eventually affecting other organs, such as the liver and the brain.[49-51] ALL is one of the two main types of acute leukaemia and is a cancer of the white blood cells (WBC), which are involved in immune function. ALL results in immature and poorly differentiated cells, known as blasts.[49, 52] Although ALL is a rare disease, it represents the most common type of childhood cancer, with around 54% of cases diagnosed in patients under the age of 14.[53] Adults account for only around 40% of ALL cases[52] but 80% of ALL deaths[43], suggesting a more aggressive course of the disease when diagnosed in adults, as adults are more likely to present with unfavourable cytogenetic abnormalities or be unable to tolerate the intensive treatment options.[54]

ALL is classified by the World Health Organisation (WHO) based on the maturity and type of lymphoblast (B- or T-cell) that leukaemic cells are derived from, known as the 'immunophenotype' of the leukaemia.[40, 51] A breakdown of the classification of ALL is presented in Figure 4. This submission is concerned with B-cell ALL, which is the most commonly occurring type of ALL.[55] A UK based study estimated that B-cell ALL accounted for around 82% of all ALL cases.[41]

ALL can also be classified by the status of the Philadelphia chromosome, an abnormal version of chromosome 22, which incorporates a section of chromosome 9, and this classification has an effect on prognosis and treatment.[56] The prevalence of the Philadelphia (Ph) chromosome is linked to age, and is one of the most common genetic abnormalities in adult ALL. In patients with ALL aged 18–35 years, around 12% are Ph-positive (Ph+), whereas in patients with ALL aged 36–50 years, 40% are Ph+, with this figure rising to 50% for patients with ALL aged over 60 years.[57, 58] Conversely, Ph+ ALL is relatively uncommon in paediatric patients, accounting for only around 3% of ALL cases.[59] Ph+ B-cell ALL is associated with poorer outcomes, and its increased prevalence in older patients (along with other unfavourable cytogenetic abnormalities) may explain why these patients generally have a worse prognosis than paediatric patients.[54] However, treatment with inotuzumab does not require the sub-classification of [redacted] (see draft SPC in Appendix 1).[1]

Figure 4: Classification of ALL



Key: ALL, acute lymphoblastic leukaemia; Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative.
Notes: * The prevalence of Ph+ B-cell ALL increases with increasing age.[57]
Figures for breakdown of B-cell and T-cell ALL are approximate for adult ALL[55]
Source: Basson et al. (2004)[55]

Due to the characteristic protein expression associated with leukaemic cells, ALL may also be classified by the protein expression profile. Normal B-lymphocytes undergo a characteristic process of development, differentiation and maturation, in which the cells are programmed to produce antibody responses against specific antigens.[60] Throughout this process the cells express antigen receptors on their surface specific to their developmental stage. As malignant B-cells go into developmental arrest while still immature and are prevented from reaching maturation, sustained expression of early developmental antigens is characteristic of leukaemic cells.[61, 62] Understanding the expression patterns of these proteins is important for the development of novel, targeted therapies, such as those utilising specific antibodies.[60]

The antigen CD22 is expressed on the surface of the leukaemic cells in over 90% of B-cell ALL cases.[47, 63] CD22 expression is switched off upon activation of normal mature cells and is not expressed on haematopoietic stem cells or other cell types.[47, 63] These characteristics, alongside the fact that CD22 is not shed from the cell

membrane, but is instead rapidly internalised to the interior cell, makes it an ideal target for antibody-mediated therapy.[30]

ALL is considered a multi-factorial disease, with many different factors contributing to its development.[40, 52] The aetiology of ALL remains undetermined, and supporting data for various risk factors (thought to include environmental, dietary and maternal factors) are inconsistent and contradictory.[40, 50]

Irrespective of the causal factors, ALL is known to be the result of the malignant transformation of progenitor WBCs, known as lymphoblasts; specifically those destined to become B- and T-lymphocytes.[61, 64] There is a distinct genetic diversity present in diagnostic ALL samples, with many different identified mutations.[62] This diversity evolves as the disease progresses, with mutations being lost and acquired over time. Initiation of chemotherapy influences this evolution, destroying leukaemic cells and driving selection for mutations that confer resistance to therapy.[62] This development of resistance can lead to relapse of the disease.[62]

The main aim of treatment in B-cell ALL is to get patients into remission so that they can receive additional treatment, such as HSCT, that can potentially cure the patient and therefore lead to long-term survival benefits. As described in Table 5, the outcomes used to indicate that a patient is able to receive these additional treatments are CR or CRi, preferably with MRD-negativity, as MRD-negativity is associated with better outcomes, which will be captured in terms of improvements in OS.[45, 46]

Table 5: Definitions of ALL treatment objectives

Outcome	Definition
CR	<5% of blasts in the bone marrow and the absence of blood leukaemic blasts, full recovery of peripheral blood counts and resolution of any extramedullary disease.
CRi	<5% of blasts in the bone marrow and the absence of blood leukaemic blasts, partial recovery of peripheral blood counts and resolution of any extramedullary disease.
MRD negativity	Having no minimal residual disease is defined as having less than 1 x 10^{-4} (<0.01%) detectable leukaemic cells in bone marrow samples.

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; MRD, minimal residual disease.
Source: Hoelzer et al. (2015)[65], NCCN (2015)[66]; Appelbaum et al. (2007)[67]

However, in current practice, after initial treatment, approximately 44% of adult patients with ALL are expected to experience disease relapse, with a further 4% demonstrated to be treatment refractory[41], although the number of patients relapsing may be as high as 60–70%.[42] In general, patients with R/R B-cell ALL are associated with the poorest outcomes.[68-71] Long-term disease-free survival after initial treatment is only achieved in a small minority of these adult patients[40], and OS may be as low as 3 months.[11-13] Furthermore, in patients with R/R B-cell ALL the probability of survival 3 years after relapse was shown in a study to be 46% if CR is achieved at first salvage (i.e. first treatment following relapse or failure to respond to induction therapy [refractory disease]), which falls to 36% if CR is achieved at second salvage.[14] However, if a patient fails to achieve CR at either first or second salvage, the probability of survival 3 years after relapse falls even further, to 8% and 3%, respectively.[14] It should be noted, though, that the patients in this study were much younger than those in inotuzumab's INO-VATE 1022 trial and in UK practice, so could be expected to have performed better.

3.2 Effect of disease on patients, carers and society

ALL often manifests as a variety of non-specific symptoms, including fatigue, fever, weight-loss, dyspnoea (difficulty breathing), dizziness, increased rate of infection, and augmented bruising or bleeding.[49, 50, 64] Central nervous system (CNS) involvement occurs in around 10% of cases (more commonly in patients with B-cell ALL), with specific symptoms including headache, vomiting, fatigue and facial numbness.[50, 72, 73] Enlarged lymph nodes, liver and spleen occur in around 20% of patients, particularly those with mature B-cell ALL, but are commonly asymptomatic.[72]

Despite the extensive literature describing the HRQL of cancer patients, given the rarity of this disease, there is limited evidence to illustrate the HRQL burden in patients with R/R B-cell ALL and their caregivers. These patients typically experience poor HRQL, demonstrating impairments in specific assessment domains including role, physical and social functioning.[74-77] Patients with high-risk ALL (i.e., those with a worse prognosis) commonly experienced psychological and physical problems, particularly relating to emotion, cognition and pain.[76] They were also demonstrated to

have poorer HRQL scores than standard-risk patients, due to increased relapse rates and the necessity for HSCT.[76]

Patients with R/R B-cell ALL are generally treated with chemotherapy, which requires patients to stay in hospital to receive treatment and to monitor side-effects, all of which further impacts HRQL, both on a short- and long-term basis. The most common side effects of treatment include fatigue, depression and anxiety, which often lead to impaired physical function (and in some severe cases even symptoms of post-traumatic stress disorder).[78] The symptoms associated with treatment can seriously interfere with a patient's ability to conduct a normal life, and can affect not only their HRQL but also their ability to perform regular daily activities (such as eating), particularly during periods of treatment.[78]

Following treatment, many patients that do manage to achieve remission feel that their HRQL improves; they feel that they have a new appreciation for the value of life and readjust their priorities accordingly, which outweighs any negative consequences of treatment.[79] However, there are also some patients that report a poorer psychological HRQL on achieving remission, driven by feelings of being out of control.[79] These conflicting reports may make it difficult for HRQL instruments to capture some of the potential benefits or downfalls of treatment for R/R B-cell ALL patients.

The bulk of studies investigating HRQL after HSCT tend to focus on its negative impact; it is an intense treatment associated with numerous acute and late occurring physical complications, threats to HRQL, impairments in cognitive and psychological functioning, as well as impacts on relationships.[80] As the aim of treatment for R/R B-cell ALL is for patients to achieve CR/CRi in order to be able to receive HSCT, the negative impacts of this subsequent treatment may complicate any analysis of HRQL. However, the benefits of HSCT are in its potential to cure, with long-term survival benefits. Following HSCT, once patients are in recovery, prompt improvements are then seen with overall HRQL largely returning to or surpassing baseline values within 100 days[81-83] and demonstrating ongoing moderate to large improvements in the long-term.[81, 82, 84-88] Therefore, although it is an intense treatment option, there are long-term benefits for those who are able to receive it. The issue with current therapy options in R/R B-cell ALL is that few patients are able to achieve CR/CRi (although they still have to experience the intense treatment

options), and therefore, fewer patients progress to HSCT, to reach these long-term benefits.

Adults with R/R B-cell ALL are generally of working age, and therefore also face increased absenteeism (due to missing work for treatment or being too ill to work), and presenteeism (being unable to perform to the best of their ability while at work), which will also potentially have wider societal implications in terms of reduced output. Patients may also experience a high degree of financial difficulty, related to both lost income due to the reduced ability to work, and costs associated with treatment, which may even include relocation.[74, 76]

In addition to care provided by healthcare professionals, patients with ALL often require informal care from their family or caregivers, particularly during periods when they are not hospitalised. Caring for adult patients with leukaemia is demanding and can include physical and emotional support, performing of household tasks and managing finances.[89] As a result, caregivers experience feelings of fear, helplessness, uncertainty about the future, being overwhelmed or feeling inadequate.[89] Caregivers themselves have identified the following factors as major influences on their HRQL: disease burden, disruption to their own lives, positive adaptation and outlook, financial concerns, and support from friends and family.[90] This burden is particularly high following HSCT, due to the need to relocate to temporary housing to receive conditioning treatment prior to transplantation and a reduced ability to work, as well as the transplant itself and the associated monitoring.[91] As such, caregivers frequently experience distress or burnout, which can manifest as anxiety, depression and emotional distress. They may also develop physical conditions including fatigue, sleep disturbance, pain, weakness, reduced appetite and weight loss.[91] In some cases caregivers even shown to display similar or higher levels of anxiety and depression than the patients themselves.[92] This impact on caregivers' psychological outcomes may also disrupt the wider family dynamic.[91]

Therefore, patients, caregivers and their families face a substantial economic and humanistic burden that significantly reduces HRQL, leading to a number of unmet psychological and social needs that could be met by improvements in patient care.

3.3 Clinical pathway of care

As discussed in Section 3.1, the aim of treatment in R/R B-cell ALL is to achieve CR or CRi (preferably with MRD-negativity), which are eligibility requirements for future, potentially curative therapies, and without undue toxicity, as each of these factors correlate with an increase in OS.[40, 46, 65, 66] Eligible patients who achieve CR or CRi, and for whom a suitable donor can be identified, may receive a potentially curative HSCT or other potentially curative treatments. However, there is also the potential to use interventions (such as inotuzumab) as a bridge to other potentially curative therapies, such as donor leukocyte infusion (DLI), which could be used in patients who have already received HSCT.[48] Ultimately, this is the goal for all eligible R/R B-cell ALL patients.[66, 93] It is important for patients to achieve not only a response to treatment, but also response with MRD-negativity, as this has been associated with improved long-term survival outcomes.[45, 46] To achieve this, therapy for R/R B-cell ALL involves salvage treatment that typically comprises of additional chemotherapy. However, with the current therapeutic options, the probability of achieving CR or CRi is only 30–40%.[14] Therefore, improved treatment options are needed for R/R B-cell ALL patients, with which a greater proportion of patients can achieve CR/CRi (preferably with MRD negativity) so that they may go on to receive further, potentially curative treatment, such as HSCT.

R/R B-cell ALL is a rare disease, and therefore, there are currently no clinical guidelines from NICE relevant to this population in NHS England. The European Society for Medical Oncology (ESMO) guidelines recommend a full diagnostic work-up for R/R B-cell ALL patients to exclude or reveal clonal aberrations and to provide bases for targeted therapies. For patients with a long first remission duration (>18/24 months) they suggest considering re-induction with the original therapy, if appropriate; for shorter first remissions durations, they recommend considering an alternative first line treatment option. The ESMO guidelines also acknowledge that there is no standard, established re-induction therapy and that new drugs are used most frequently for this patient group.[94]

Current treatment options for R/R B-cell ALL are very limited and include chemotherapy-based regimens.[48] Feedback from UK clinicians[48] and the available literature commenting on treatment practices[95] indicate that FLAG-based chemotherapy regimens are established clinical practice in the UK for the majority of

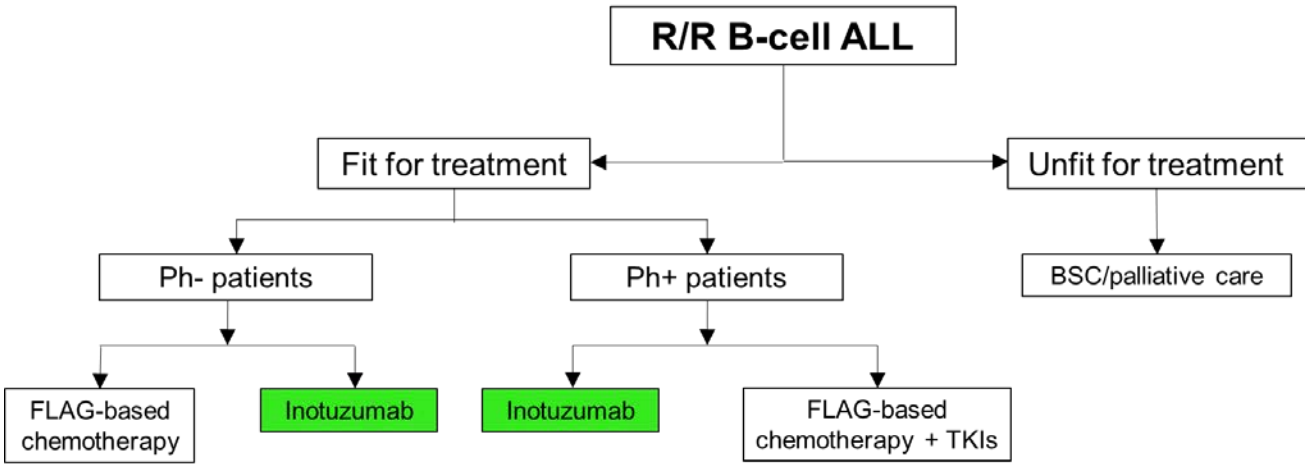
adult patients with R/R B-cell ALL. For patients who are able to receive more intensive therapy, FLAG can be given in combination with idarubicin (FLAG-IDA). However, a small study of 105 patients with poor risk acute leukaemia or myelodysplastic syndrome who were treated over a 4-year period showed no statistical difference in outcomes between FLAG and FLAG-IDA.[96] Clinicians agreed that although FLAG-IDA may be considered by some to provide more efficacy, it is also more toxic and as a result could be considered to have a similar risk-benefit profile to FLAG, meaning the two therapies could effectively be considered as equivalent.[48]

TKIs are commonly used alongside chemotherapy-based regimens for first-line treatment of Ph+ patients in UK clinical practice. There is evidence to support the use of TKIs in first-line treatment, but there is limited comparative evidence to support the use of TKIs in the R/R B-cell ALL population and limited data available to understand the market share of TKIs in this area. Although the INO-VATE 1022 study does not include TKIs, these have been incorporated into the economic model alongside chemotherapy-based treatment for Ph+ patients (see Section 5).

For patients who were unable to receive chemotherapy-based treatments, the only current option is palliative care. In the UK, palliative care varies widely and is also again based heavily upon decision-making at the individual patient level. It may include treatment to alleviate symptoms, blood and/or platelet transfusions or palliative vincristine, steroids or maintenance-style therapy.[48] However, as inotuzumab is suitable as a bridge to potentially curative therapy (usually HSCT), patients who are unfit for intensive therapy, such as chemotherapy-based treatments, will also be unfit for transplantation. Therefore, inotuzumab would also be unsuitable for these patients and palliative care would not be a relevant comparator.

Overall, expert opinion stresses that, because of the rarity of the condition and lack of guidance, the patient pathway at this point is extremely heterogeneous, and is based heavily upon decision-making at the individual patient level, emphasising the need for increased treatment options and a formal standard of care for the future. Figure 5 presents the current treatment pathway for patients with R/R B-cell ALL in England, with the proposed placement of inotuzumab.

Figure 5: Current treatment pathway with proposed placement of Inotuzumab



Key: ALL, acute lymphoblastic leukaemia; BSC, best supportive care; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; Ph-, Philadelphia chromosome negative; Ph+ Philadelphia chromosome positive; R/R, relapsed or refractory; TKI, tumour necrosis factor.
Source: Adapted from evidence provided in a clinical ad board[48] and the UKALL 14 treatment protocol[97]

Given the poor outcomes associated with current treatments, there is a clear unmet need in this rare patient population. However, due to the rarity of the condition, a lack of clinical guidance and the wide variety of treatments used in clinical practice, any new treatment being appraised in this patient population will face challenges in performing comparative clinical and economic assessments versus established clinical practice.

3.4 Life expectancy and patient population

Adults with R/R B-cell ALL experience extremely poor outcomes, with reported median OS as low as 3 months with current salvage therapies (with which there are low rates of CR/CRi), and therefore, very few patients (5 to 30%) are able to progress to potentially curative treatments.[11-13] As a result, 5-year OS in these patients is less than 10%.[12, 41] Overall, patients who do not achieve CR or CRi (preferably with MRD-negativity), who are not eligible for HSCT or other curative therapies, have poor prognosis, and without HSCT, survival is only 3 to 6 months following relapse compared to over 14 months for patients receiving HSCT.[14]

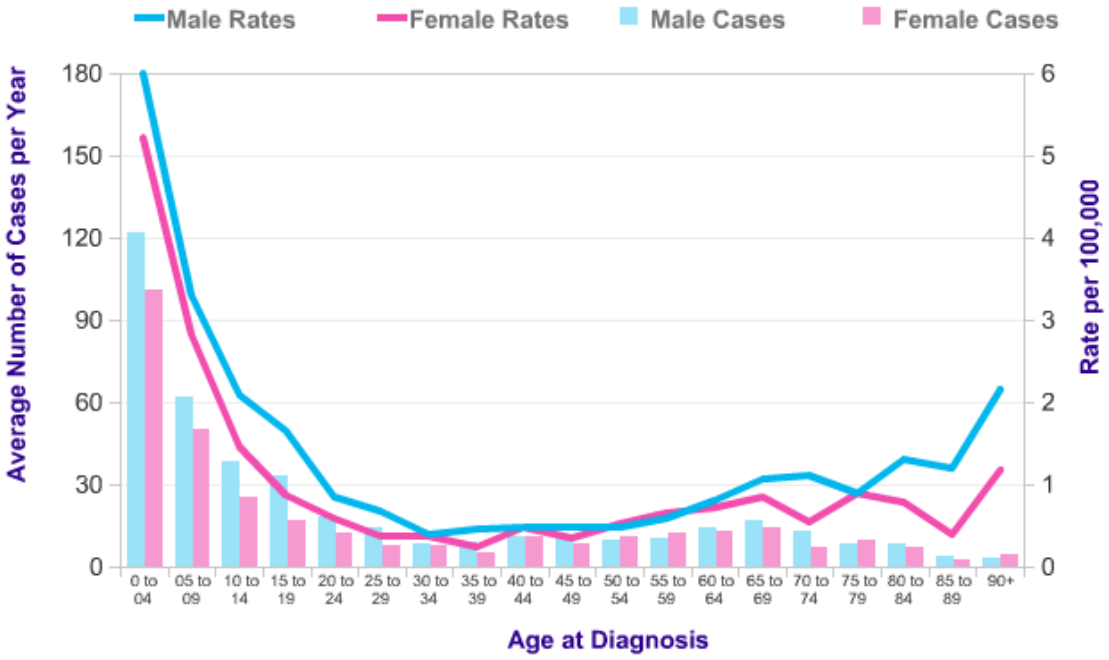
Table 6 presents survival outcomes for patients treated with current standard of care, chemotherapy for R/R B-cell ALL. From all of these sources, it is clear that with current treatment options survival time for these patients is low, and well within the 24-months required by NICE to be assessed as meeting end-of-life criteria.

Table 6: Survival in R/R B-cell ALL patients treated with standard care

Source	Outcome	Survival
INO-VATE 1022[3]	Median OS	6.7 months (95% CI: 4.9, 8.3)
	RMST OS	9.9 months (SE: 0.9)
TOWER[98]	Median OS	4 months (95% CI: 2.9, 5.3)
	Median OS, censoring for HSCT	3.9 months (95% CI: 2.8, 4.9)
O'Brien, 2008[11]	Median OS	3 months
Oriol, 2010[12]	Median OS	4.5 months
Thomas, 1999[13]	Median OS	5 months
Key: CI, confidence interval; OS, overall survival; RMST, restricted mean survival time; SE, standard error.		

Statistics provided by Cancer Research UK show that there were around 654 new cases of ALL diagnosed in England in 2014; 390 cases in males and 264 cases in females, giving a crude incidence rate of 1.5 per 100,000 males and 1.0 per 100,000 females and an overall crude incidence rate of 1.2 per 100,000 persons.[53] Across the UK, ALL comprised 0.2% of all new cancer cases and 9% of all new leukaemia cases.[53] These data also show a strong correlation between age and ALL incidence (Figure 6). Between 2011 and 2013, around 54% of ALL cases in the UK were diagnosed in patients aged 0 to 14 years.

Figure 6: New ALL cases diagnosed per year in the UK by age group; 2010–12



Key: ALL, acute lymphoblastic leukaemia.
Source: Cancer Research UK[53]

B-cell ALL is a rare but frequently fatal leukaemia. It has an incidence of approximately 1 in 100,000.[53, 99, 100] The UK Haematological Malignancy Research Network (HMRN) has reported that B-cell ALL comprises 1.4% of all haematologic malignancies in the UK, with a 10-year prevalence of 5.6 per 100,000.[101] There were 201 ALL-related deaths in 2014 in England.[53]

The population of interest for this submission is adult patients with R/R B-cell ALL. In Section 3.1, it notes that that approximately 82% of ALL patients are B-cell ALL patients.[41] Of these B-cell ALL patients, approximately 44% will experience a relapse after treatment, with an additional 4% being refractory to treatment[41], although the number of patients relapsing could be as high as 60–70%[42]; long-term disease-free survival after initial treatment is achieved in only a minority of adult patients.[40]

Inotuzumab was granted orphan designation for this population by the EMA in 2013 and therefore has an anticipated indication for a very small patient population.[38] To calculate the incidence of R/R B-cell ALL the following steps were taken:

- Newly diagnosed ALL cases in 2014 were taken from the Office of National Statistics (ONS)[102]

- These patients were multiplied by the probabilities of patients having B-cell ALL (82%)[41]
- These patients were then multiplied by the proportion of relapsed (44%) and refractory (4%) disease[41]
  - Fielding et al., (2007) was used as this study provided relevant data for a UK population.[41]
- The data were split by gender and age groups and the incidence rate was calculated by comparing the incidence population of R/R B-cell ALL against the population of England in 2014 from ONS for each age/gender subset.
- Based on these calculations, the R/R B-cell ALL population for 2017 in England is estimated to be 117 patients (see Section 6).

A flow chart detailing the calculations involved with estimating the relevant patient population for this submission is presented as part of the modelling in Figure 57 within Section 6.

3.5 Relevant NICE guidance and clinical guidelines

NICE guidance and additional clinical guidelines of relevance to this appraisal are summarised in Table 7.

Table 7: Relevant guidance and clinical guidelines

Organisation	Title	Date	Summary
NICE guidance			
NICE clinical guideline NG47	Haematological cancers: improving outcomes[103]	2016	• Guidance relating to integrated diagnostic reporting, staffing and facilities (level of care) for adults and young people who are having high-intensity non-transplant chemotherapy, the use of multidisciplinary teams and recommendations from the 2003 cancer service guidance. • No guidance for treatment is included in this guideline (treatment is only mentioned in terms of service provision and not as clinical guidance).
NICE technology appraisal TA408	Pegaspargase for treating acute lymphoblastic leukaemia[104]	2016	• Pegaspargase, as part of antineoplastic combination therapy, is recommended as an option for treating acute lymphoblastic leukaemia in children, young people and adults only when they have untreated newly diagnosed disease.
Clinical guidelines			
ESMO	Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[94]	2016	Pre-phase therapy: • Corticosteroids (usually prednisone 20–60mg/day or dexamethasone 6–16mg/day) alone or in combination with another drug (e.g. vincristine, cyclophosphamide), often together with allopurinol and hydration, is recommended immediately (usually for roughly 5–7 days) once the diagnosis is established. Treatment algorithm: • Chemotherapy included induction therapy 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2.5 years. • Ongoing chemotherapy protocols for adolescents and young adults use paediatric type regimens • Prophylactic treatment to prevent CNS relapse is mandatory Antibody therapy: • Rituximab in combination with a chemotherapy is strongly recommended for Burkitt leukaemia/lymphoma • Anti-CD22 immunoconjugates directed against CD22 currently under investigation • Bispecific (CD2/CD19) blinatumomab under investigation

Organisation	Title	Date	Summary
			• Chimaeric antigen receptor modified T cells directed against CD19 in early phase Targeted therapy with TKIs in Ph-positive ALL: • A TKI should be combined with chemotherapy in front-line therapy • The TKI imatinib (400–800mg/day) should be administered continuously, also post-HSCT • Prolonged monitoring of BCR-ABL-1 MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation TKI Allogeneic HSCT: • Allogeneic HSCT in patients with a first complete remission significantly improves OS and EFS in high-risk patients/MRD-positive patients and is the best post-remission option for Ph-positive ALL and MLL-rearranged ALL • Conditioning regimens are age-adapted with full allogeneic vs RIC for elderly patients or those unfit for full conditioning • The role of autologous HSCT should be investigated for MRD-negative patients in the setting of clinical trials • All patients in their second or later complete remission are candidates for allogeneic HSCT Relapsed/refractory ALL: • Full diagnostic work-up necessary to exclude/reveal clonal aberrations and to provide the basis for targeted therapies • Different treatment for patients with short vs long first remission duration (>18/24 months) where re-induction is considered • Treatment: there is no standard re-induction therapy established; most often new drugs are used
NCCN	Acute lymphoblastic leukaemia: NCCN guidelines for patients[105]	2016	Induction treatment: • For adolescents and young adults with Ph-negative ALL, treatment with a paediatric-inspired chemotherapy regimen (which tend to use a combination of vincristine, pegaspargase, a steroid (prednisone or dexamethasone) and an anthracycline (doxorubicin or daunorubicin), but may also include cyclophosphamide and etoposide) are preferred. Enrolment in a clinical trial or another multiagent chemotherapy regimen are also options for this group. • For older adults with Ph-negative ALL, enrolment in a clinical trial is preferred (if one is open and the right fit), but options also include a multiagent chemotherapy regimen for adults (or

Organisation	Title	Date	Summary
			corticosteroids for patients ≥65 years of age). • For adolescents and young adults with Ph-positive ALL, enrolment in a clinical trial is preferred (if one is open and the right fit). The other option is a paediatric-inspired multiagent chemotherapy regimen combined with a TKI, such as imatinib or dasatinib. • For older adults with Ph-positive ALL, enrolment in a clinical trial is preferred (if one is open and the right fit). The other option is a multiagent chemotherapy regimen combined with a TKI, such as imatinib or dasatinib (or corticosteroids combined with a TKI in patients ≥65 years of age). • CNS preventive treatment is given to all patients during induction and may include intrathecal (IT) methotrexate alone or in combination with IT cytarabine and an IT steroid, such as dexamethasone or prednisone. Methotrexate, cytarabine and 6-MP may also be given as IV injections for CNS treatment. Consolidation therapy for patients in remission: • For patients with Ph-negative ALL, the two main options are to continue their multiagent chemotherapy option, usually at higher (intensified) doses (may be an especially good option if no leukaemia cells were found by MRD testing) or to consider an allogeneic HSCT • For patients with Ph-positive ALL, the recommended option is to have an allogeneic HSCT, if a well-matched donor has been found. Other patients should continue their multiagent chemotherapy (at an intensified dose) combined with a TKI (or continue on corticosteroids plus a TKI in patients ≥65 years of age who received this for induction). • Allogeneic SCT is not recommended for patients aged ≥65 years, or those with other serious health problems. Maintenance therapy for patients in remission: • Patients who received an allogeneic HSCT will begin follow-up testing • For patients with Ph-positive ALL who received an allogeneic HSCT, maintenance therapy with a TKI is recommended, either alone or with other drugs if the side effects are not too severe. • Patients who continued their intensified induction regimen will receive maintenance therapy to prevent relapse. Usually based on a backbone of daily 6-MP and weekly methotrexate, and often vincristine and a steroid (methotrexate or dexamethasone) are also given. Maintenance is given for 2–3 years, depending on the treatment used, but paediatric regimens tend to be given for a longer time than adult regimens. Patients with Ph-positive ALL are also recommended to receive a TKI for maintenance. Relapsed and refractory ALL:

Organisation	Title	Date	Summary
			• The preferred treatment option is enrolment within a clinical trial (if one is open and the right fit). A second option is to have a different induction regimen (relevant to the specific patient type) than was used previously (or the same regimen can also be considered for late relapsing [over 3 years from diagnosis] adolescents and young adults). • Another option for Ph-negative ALL patients (or Ph-positive patients who did not respond to TKIs) is chemotherapy for relapsed or refractory ALL: o Blinatumomab is the preferred option for B-cell ALL[a] • An allogeneic HSCT is an option if a matched donor has been found and the patient is considered healthy enough to tolerate the treatment. If ALL relapses after an initial allogeneic HSCT, a second allogeneic HSCT is an option, or a donor lymphocyte infusion could be considered.
Key: 6-MP, 6-mercaptopurine; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; EFS, event-free survival; ESMO, European Society for Medical Oncology; HSCT, haematopoietic stem cell transplant; IT, intrathecal; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; OS, overall survival; RIC, reduced-intensity conditioning; TKI, tyrosine kinase inhibitor. **Notes:** [a] NICE has not yet produced guidance on the use of Blinatumomab and is therefore not currently used as part of standard practice in NHS England.			

3.6 Issues relating to clinical practice

As outlined in Section 3.3, the aim of treatment in R/R B-cell ALL is to achieve CR/CRi, preferably with MRD-negativity, to improve long-term outcomes.[45] CR/CRi are signals for future, potentially curative therapies, which therefore result in survival benefits for patients, and MRD-negativity further improves these outcomes.[45, 46] However, there is currently very limited guidance available on how to treat patients with R/R B-cell ALL in order to achieve this goal. Expert opinion highlights that the patient pathway at this point is extremely heterogeneous and is based heavily upon decision-making at the individual patient level.[48] Indeed, the evidence base for existing treatments in this population is limited (as shown by the clinical SLR; see Section 4.1), with few RCTs in existence because of the high fatality rate[106] (median OS of 24 weeks[41]) and the very small patient population.

In accordance with the lack of guidance, current treatment options for R/R B-cell ALL are very limited and mainly include chemotherapy-based treatments, as seen in the final scope for this appraisal and confirmed by clinical experts.[48] Chemotherapies are associated with significant toxicities, including haemato-, hepato-, nephro- and neuro-toxicities, risk of infection and mucositis.[107] They are also usually administered in an inpatient setting and require lengthy hospital stays for disease management and AE monitoring, which can have a severe impact on the patients HRQL.

For patients who are unable to receive chemotherapy, options are limited to palliative care; including treatment of symptoms, blood and/or platelet transfusions or other palliative therapy. Patients receiving palliative care are not expecting to survive long; often no more than 1–2 weeks or less.[48]

Therefore, given the issues with current treatment used for R/R B-cell ALL, there is a clear unmet need for additional treatment options for these patients to not only improve outcomes, but to provide a clear, unformed, standard of care for England and Wales.

3.7 Equality

No equality issues related to the use of inotuzumab have been identified or are foreseen.

4. Clinical effectiveness

Summary of Clinical Evidence

Direct head-to-head evidence from INO-VATE 1022 demonstrates the clinical benefit of inotuzumab compared with chemotherapy-based standard of care for R/R B-cell ALL

- The INO-VATE 1022 Phase III RCT provides evidence in a patient population that directly matches that specified in the decision problem.
- This trial provides direct head-to-head evidence from 326 patients randomly assigned to either inotuzumab (n=164) or the investigator's choice (n= 162) of: FLAG (n=102), cytarabine plus mitoxantrone (n=38), or high-dose cytarabine (n=22).
- UK clinical experts agreed the trial comparator was appropriate for consideration in the UK context, as the majority of patients received FLAG-based chemotherapy as per UK clinical practice.
- Significantly more patients treated with inotuzumab achieved CR/CRi than in the control arm:
  - ITT218 population (primary analysis): 80.7% (95% CI: 72.1, 87.7) versus 29.4% (95% CI: 21.0–38.8), respectively (rate difference = 51.4% [97.5% CI: 38.4, 64.3]; p<0.0001)
- Significantly more patients treated with inotuzumab proceeded to receive subsequent HSCT: [redacted]% in the inotuzumab arm compared with [redacted]% in the control arm (p[redacted]).
- Significantly more patients treated with inotuzumab achieved MRD-negativity, a prognostic factor for longer term outcomes. Among patients achieving CR/CRi, [redacted]% achieved MRD negativity in the inotuzumab arm vs. [redacted]% in the control arm (p[redacted]).
- The estimated HR for OS (stratified) was 0.77 (97.5% CI: 0.58, 1.03; p=0.0203) in favour of inotuzumab and median OS was 7.7 months (95% CI: 6.0–9.2) in the inotuzumab arm compared with 6.7 months (95% CI: 4.9–8.3) in the control arm. However, there was non-proportionality between the two survival curves and significant confounding of subsequent treatments received by the control arm.
- The benefit in OS was observed past the median, as a proportion of patients bridge to potentially curative therapy, therefore OS as calculated by restricted mean survival time (RMST) analysis is a more appropriate metric of inotuzumab benefit than median OS and HR.
- The RMST OS was 13.9 months (SE: 1.1) for inotuzumab compared with 9.9 months (SE: 0.9), for standard of care, a gain of 3.9 months (95% CI: 1.2–6.7) in life expectancy (p=0.0023).
- Inotuzumab significantly improved PFS; 5.0 months (95% CI: 3.7–5.6) versus 1.8 months (95% CI: 1.5–2.2), respectively (HR, stratified = 0.45 [97.5% CI: 0.34, 0.61]; p<0.0001).

The INO-VATE 1022 trial demonstrated that inotuzumab was associated with improved quality of life and a more favourable adverse events profile than standard of care

- Inotuzumab was shown to significantly improve patients HRQL, as assessed by the EORTC QLQ-C30.
- Inotuzumab patients had better appetite, were more ambulatory, and experienced significantly less impact on family and social life (estimated mean treatment difference >5 points, p<0.05), compared with standard of care.
- The HRQL burden in R/R ALL with current SoC is evidenced by the poor HRQL in the control arm the INO-VATE 1022 trial.
- Inotuzumab demonstrated a more favourable toxicity profile, with fewer SAEs and fewer pre-specified AEs of interest than reported in the control arm.

4.1 Identification and selection of relevant studies

4.1.1. Search strategy

A systematic literature review (SLR) was designed to identify all relevant comparative studies of specified interventions used in the treatment of R/R B-cell ALL. This SLR was conducted in accordance with NICE guidelines.

The following databases were searched as standard evidence sources for clinical, safety and HRQL data used in international health technology assessments (HTAs):

- MEDLINE and Embase (using Embase.com)
- MEDLINE-In Process (using Pubmed.com)
- The Cochrane library, including the following:
  - The Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effectiveness
  - Cochrane Central Register of Controlled Trials
  - Health Technology Assessment Database

Electronic searches in the literature databases were not limited by date. All relevant studies published in English were included in this review. Studies published in non-English languages were included and flagged. These studies were to be explored if sufficient data from English language studies were not available.

Full details of the search strategy used for clinical effectiveness searches are provided in Appendix 2.

Bibliographies of key SLRs and meta-analyses were also screened to ensure that our initial searches had captured all of the relevant clinical studies.

Hand searches of conference proceedings were performed to identify recently completed or ongoing studies of interest. These searches were restricted to the last 3 years (2014-2016) and covered the following conferences:

- American Society for Haematology (ASH)
- American Society of Clinical Oncology (ASCO)

- British Society for Haematology (BSH)
- European Haematology Association (EHA)

Additional searches to identify any relevant data were made on the HTA websites listed below:

- European Medicines agency (EMA) (http://www.ema.europa.eu/ema/)
- US Food and Drugs Administration (FDA) (http://www.fda.gov/)
- NICE (http://www.nice.org.uk/)
- Canadian Agency for Drugs and Technologies in Health (CADTH) (http://cadth.ca/en/products)
- SMC (http://www.scottishmedicines.org.uk/Home)
- All Wales Medicines Strategy Group (AWMSG) (http://www.wales.nhs.uk/sites3/home.cfm?orgid=371)

4.1.2. Study selection

Titles and abstracts (where available) were reviewed by two independent reviewers and assessed for inclusion according to the list of pre-specified inclusion/exclusion criteria, presented in Table 8. Articles that were identified as potentially relevant during the first phase of the screening were then retrieved and reviewed in full by two independent reviewers against the same pre-specified inclusion/exclusion criteria. Any discrepancies were resolved through discussion and/or involvement of a third reviewer.

Table 8: Eligibility criteria applied to systematic search results

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients aged at least 15 years[a] Patients diagnosed with Relapsed OR Refractory ALL	Paediatric patients Patients with newly diagnosed ALL Adolescents with R/R ALL receiving Paediatric treatment regimen
Line of therapy	No restriction Patients receiving treatments for R/R ALL will be included	

Criteria	Inclusion criteria	Exclusion criteria
Study design	RCTs of any design Non-RCTs including comparative observational studies SLRs and meta-analyses of RCTs[b]	Preclinical studies Comments, letters, editorials Case reports, case series Single arm studies
Interventions	Inotuzumab Blinatumomab Dasatinib Imatinib Ponatinib Clofarabine FLAG FLAG-IDA HIDAC (high dose cytarabine) Ara-C plus mitoxantrone Methotrexate Asparaginase Daunorubicin Cyclophosphamide Vincristine Mercaptopurine Pegaspargase Doxorubicin Hyper-CVAD	
Comparators	Placebo Best supportive care (as reported in articles/studies) Any treatment from the list above	Any pharmacological treatment not mentioned in the list of included interventions Any non-pharmacological treatment
Outcome	The studies must report relevant data (or sufficient information to allow the calculation of relevant data). The tentative list of outcome includes: Overall survival Progression-free survival Time to progression Time to response Overall response Complete response Partial response Stable disease Progressive disease HRQL Tolerability Adverse events	

Criteria	Inclusion criteria	Exclusion criteria
Language	Studies published in English will be included Studies not published in English will be included and flagged	Studies will not be excluded on the basis of publication language
Key: ALL, acute lymphoblastic leukaemia; HRQL, health-related quality of life; SMC, Scottish Medicines Consortium; RCTs, randomised controlled trials; RR ALL, relapsed or refractory acute lymphoblastic leukaemia; SLR, systematic literature review. **Note:** [a] Patients who were ≥15 years were included for completion as in R/R ALL they may be treated with the treatment regimen recommended for adults; [b] SLRs and meta-analyses of RCTs will be included and flagged. Bibliographies of these systematic reviews will be screened to check if literature searches have missed any potentially relevant studies.		

The criteria used in the SLR were broader than those required for this submission, and therefore the results of the SLR were further screened to identify studies that were specifically of interest to the NICE scope.

Data were extracted from the included full text article by one reviewer, and all extracted data verified against the original source paper by a second reviewer. Any query raised during the quality check was resolved through discussion and/or involvement of a third reviewer.

A descriptive quality assessment of the included randomised controlled trials (RCTs) was performed by two independent reviewers using comprehensive assessment criteria based on the recommendations in the NICE manufacturer's submission template and the quality assessment of the included non-RCTs was performed using a checklist by Downs and Black.[108]

4.1.3. Search results

Initial electronic database searches and website searches were conducted on 27 September 2016. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the initial review is presented in Figure 7.

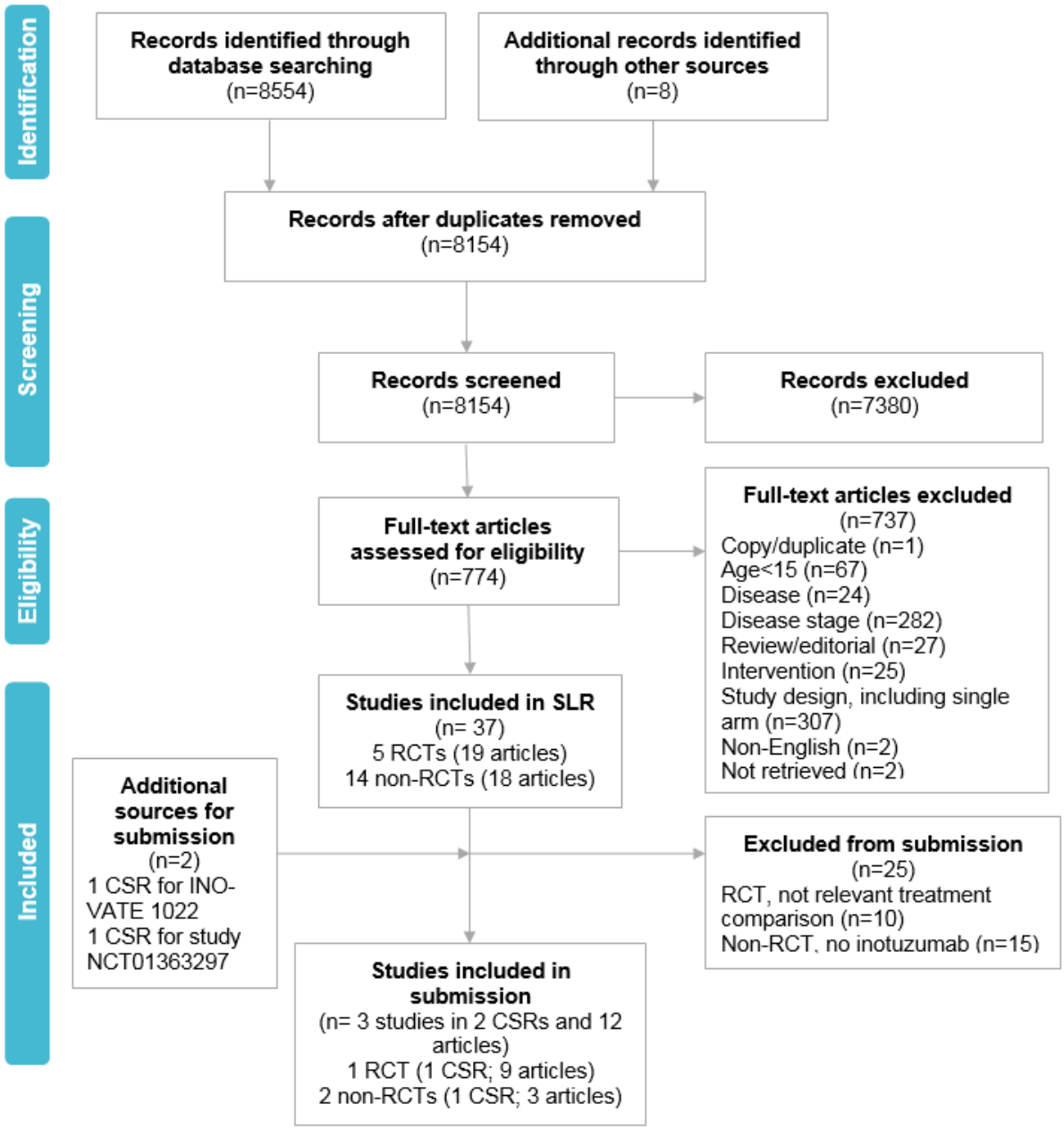
A total of 8,554 citations were captured from the electronic database searches, and 8 additional publications were identified through manual searches. After removal of 408 duplicates, there were 8,154 citations remaining. The titles and abstracts of these citations were screened for eligibility and 7,380 references were excluded. The

full-text publications of 774 references were ordered and further screened to assess their eligibility for inclusion.

After exclusion of publications that did not meet the selection criteria, 19 publications reporting the results of 5 RCTs, and 18 publications reporting the results of 14 non-RCTs were included in the SLR (Figure 7).

As the objectives of the SLR were broader than the requirements for this submission these results were further screened to identify references of studies that were relevant to the decision problem. Only two studies that presented evidence that was directly relevant to the decision problem for this submission were identified by the SLR; one RCT (INO-VATE 1022) and one non-RCT (the MDACC study). One additional non-randomised study for inotuzumab (NCT01363297) was identified, but would not have been included in the SLR as study results had only been published in abstracts that were outside the search dates of the SLR. As this provides additional evidence for inotuzumab the CSR for this study has been included in the submission, as additional support for the INO-VATE 1022 trial.

Figure 7: PRISMA flow diagram of the SLR search process



Key: RCT, randomised controlled trial
Source: Adapted from Moher et al. (2009)[109]

Table 9 presents a list of the studies included in the submission, the primary and secondary references for each study and where the evidence is presented within the submission.

Table 9: Studies included in the submission

Study	Primary Reference(s)	Secondary Reference(s)	Evidence presented in the submission
INO-VATE 1022	INO-VATE 1022 CSR[3]; Kantarjian, 2016[2]	Jabbour, 2016[110]; Kantarjian, 2016[111]; DeAngelo, 2016[17]; DeAngelo, 2015[112]; Kantarjian, 2016[113]; DeAngelo, 2016[114]; Jabbour, 2016[115]; Kantarjian, 2016[77]	Section 4.2 through Section 4.8 (efficacy results in Section 4.7) and Section 4.12 (safety)
NCT01363297	NCT01363297 CSR[116]	Not applicable	Section 4.11
MDACC study	Kantarjian, 2013[63]	Jabbour, 2015[117]; Jabbour, 2016[44]	Section 4.11

4.2 List of relevant randomised controlled trials

The INO-VATE 1022 trial is the pivotal, regulatory Phase III RCT that provides data for inotuzumab in adult patients with R/R B-cell ALL (Table 10). This trial compares inotuzumab to standard of care (SoC), which was defined as investigators' choice of one of three regimens: FLAG; cytarabine plus mitoxantrone (CM); or high dose cytarabine (HIDAC). The majority of patients within the control arm of the trial received FLAG treatment (63%), which clinical experts have advised is reflective of UK clinical practice, thereby rendering the results of INO-VATE 1022 comparison sufficiently generalisable to the UK.[48]

Table 10: List of relevant RCTs

Trial name (NCT number)	Population	Intervention	Comparator	Primary study reference
INO-VATE 1022	Patients with relapsed or refractory, CD22 positive ALL	**Inotuzumab ozogamicin (N = 164)** [Patients who achieved complete remission could undergo HSCT at the investigator's discretion.]	**SoC (N = 162)** Investigator's choice of one of the following 3 regimens: • FLAG (N=102) • Cytarabine plus mitoxantrone (N=38) • High dose cytarabine (N=22) [Patients who achieved complete remission could undergo HSCT at the investigator's discretion.]	CSR[3]

Key: ALL, acute lymphoblastic leukaemia; CSR, clinical study report; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HSCT, haematopoietic stem cell transplantation; SoC, standard of care.

4.3 Summary of methodology of the relevant randomised controlled trials

A summary of the methodology used in the INO-VATE 1022 trial is presented in Table 11.

INO-VATE 1022 was a global, multicentre (including eight sites in the UK), Phase III, randomised, open-label, 2-arm study that enrolled adult patients (aged ≥18) with R/R CD22-positive ALL due to receive either first or second salvage therapy (i.e., first or second treatment following relapse or failure to respond to induction therapy [refractory disease]), and for whom either arm of randomised study therapy offered a reasonable treatment option.

To be representative of the typical patient population seen in clinical practice, the number of patients recruited that were due to receive treatment as a second salvage therapy was limited to 33% of the entire patient population, and the number of Ph+ patients was limited to approximately 20% of the overall patient population. However, as the prevalence of Ph+ ALL is typically lower than the prevalence of Ph- ALL[57, 58],

enrolment of Ph+ ALL patients did not reach the 20% cap, meaning no patients were excluded on the basis of Ph-positivity. Ph+ patients were also required to have failed treatment with at least one second- or third-generation tyrosine kinase inhibitor and standard multi-agent induction therapy, which is in line with how these patients would be treated in standard clinical practice in the NHS in England and Wales.

Patients were randomised in a 1:1 ratio (stratified by duration of first remission [<12 months vs ≥12 months], salvage-treatment phase [first vs second] and age [<55 vs ≥55]) to receive either inotuzumab 1.8mg/m^2 per cycle (in a fractionated schedule of 0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15) or an investigators' choice of one of the three regimens as discussed in Section 4.2 and presented in Table 11. The administration of inotuzumab is line with the expected license. Patients were allowed to receive concomitant medication for current medical conditions, as well as G-CSF for supportive care, in line with local guidelines and medical practice, and were strongly encouraged to receive CNS prophylaxis/treatment (e.g. intrathecal methotrexate), as these would be considered standard practice for ALL patients.

Table 11: Summary of INO-VATE 1022 methodology

Study	INO-VATE 1022
Location	The study was initiated at 193 centres in Argentina, Australia, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Finland, France, Germany, Hungary, Italy, Japan, Republic of Korea, Netherlands, Poland, Serbia, Singapore, Slovakia, Spain, Sweden, Taiwan, UK (8 sites), and the US. Of these, 129 centres screened or treated at least 1 patient.
Trial design	Phase III, randomised, multicentre, global, open-label, two-group trial. Randomisation was stratified by duration of first remission (<12 months vs ≥12 months), salvage-treatment phase (first vs second) and age (<55 vs ≥55).
Eligibility criteria for participants	**Inclusion criteria were:** • Relapsed or refractory CD22-positive ALL (≥5% marrow blasts, assessed by morphology; i.e. M2 or M3 marrow) due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option • Patients with Ph+ ALL must have failed treatment with at least 1 second- or third-generation TKI and standard multi-agent induction chemotherapy • Patients in Salvage 1 with late relapse deemed poor candidates for reinduction with initial therapy • Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment • Aged 18 years or older • Eastern Cooperative Oncology Group (ECOG) performance status 0–2 • Adequate liver function, including total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless the patient had documented Gilbert syndrome, and AST and ALT ≤2.5 × ULN. If organ function abnormalities were considered due to tumour, total serum bilirubin had to be ≤2 × ULN and AST/ALT ≤2.5 × ULN • Serum creatinine ≤1.5 × ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 ml/minute • Male and female patients of childbearing potential and at risk for pregnancy had to agree to use a highly effective method of contraception throughout the study and for a minimum of 90 days after the last dose of assigned treatment. A patient was of childbearing potential if, in the opinion of the Investigator, he/she was biologically capable of having children and was sexually active. Female patients who were not of childbearing potential (i.e. met at least 1 of the following criteria): o Had undergone hysterectomy or bilateral oophorectomy; or o Had medically confirmed ovarian failure; or o Were medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause)

Study	INO-VATE 1022
	• Evidence of a personally signed and dated Informed Consent Document (ICD) indicating that the patient had been informed of all pertinent aspects of the study; patients with mental capacity that required the presence of a legally authorised representative were excluded from the study • Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures **Exclusion criteria were:** • Isolated extramedullary relapse (i.e. testicular or CNS) • Burkitt's or mixed phenotype acute leukaemia based on the World Health Organization (WHO) 2008 criteria • Active CNS leukaemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid, use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukaemia (i.e. cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication was not a reason for exclusion • Prior chemotherapy within 2 weeks before randomisation with the following exceptions: o To reduce the circulating lymphoblast count or palliation: i.e. steroids, hydroxyurea or vincristine o For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or TKIs • Patients must have recovered from acute non-haematologic toxicity (to ≤Grade 1) of all previous therapy prior to enrolment • Prior monoclonal antibodies within 6 weeks of randomisation, with the exception of rituximab that must have been discontinued at least 2 weeks prior to randomisation • Prior allogeneic HSCT or other anti-CD22 immunotherapy ≤4 months before randomisation. Patients must have completed immunosuppression therapy for treatment of graft versus host disease (GvHD) prior to enrolment. At randomisation, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD • Peripheral absolute lymphoblast count ≥10,000/µL (treatment with hydroxyurea and/or steroids/vincristine was permitted within 2 weeks of randomisation to reduce the white blood cell [WBC] count) • Known systemic vasculitides (e.g. Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as human immunodeficiency virus [HIV] infection or severe inflammatory disease) • Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for HIV. HIV testing was performed in accordance with local regulations or local practice • Major surgery within ≤4 weeks before randomisation • Unstable or severe uncontrolled medical condition (e.g. unstable cardiac function or unstable pulmonary condition) • Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localised prostate cancer that had definitely been treated with radiation or surgery. Patients with previous malignancies were eligible provided that they had been disease-free for ≥2 years • Cardiac function, as measured by left ventricular ejection fraction (LVEF) that was less than 45%, or the presence of New York

Study	INO-VATE 1022
	Heart Association (NYHA) Stage III or IV congestive heart failure • Patients with active heart disease (NYHA class ≥3 as assessed by history and physical examination) • QTcF >470 msec (based on the average of 3 consecutive ECGs) • Myocardial infarction ≤6 months before randomisation • History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of atrioventricular (AV) block unless a permanent pacemaker had been implanted • Uncontrolled electrolyte disorders that could have compounded the effects of a QT interval (corrected for heart rate [QTc]) prolonging drug (e.g. hypokalaemia, hypocalcaemia, hypomagnesemia) • History of chronic liver disease (e.g. cirrhosis) or suspected alcohol abuse • History of hepatic VOD • Administration of live vaccine ≤6 weeks before randomisation • Evidence of uncontrolled current serious active infection (including sepsis, bacteraemia, fungaemia) or patients with a recent history (within 4 months) of deep tissue infections such as fasciitis or osteomyelitis • Patients who had a severe allergic reaction or anaphylactic reaction to any humanised monoclonal antibodies • Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for a minimum of 90 days after the last dose of study drug (inotuzumab ozogamicin) • Patients who were investigational site staff members or relatives of those site staff members or patients who were Pfizer employees directly involved in the conduct of the study • Participation in other studies involving investigational drug(s) (Phase I-IV) within 2 weeks from randomisation to EOT visit • Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration or may have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study
Settings and location where the data were collected	Project management, data management, clinical monitoring, site monitoring, data programming, and medical writing were performed by ICON plc. Biostatistical analyses were performed by ICON. This study used an external Data Monitoring Committee (eDMC), an external Hepatic Events Adjudication Board (HEAB) and an Endpoint Adjudication Committee (EAC).
Trial drugs	**InO:** Patients received inotuzumab at a starting dose of 1.8mg/m^2 per cycle (0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15). Cycle 1 lasted for 21 days, up to 28 days if necessary for toxicity recovery, and each subsequent cycle lasted for 28 days. Patients received treatment for up to 6 cycles. Once a patient achieved complete remission or complete remission with incomplete

Study	INO-VATE 1022
	haematologic recovery, the Day 1 dose was reduced to 0.5mg/m^2 for the duration of the trial. **Standard-therapy:** Investigator's choice of one of the following 3 regimens: • FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor) therapy for up to four 28-day cycles (with cytarabine at a dose of 2.0g/m^2 per day on Days 1–6, fludarabine at a dose of 30mg/m^2 per day on Days 2–6, and granulocyte colony-stimulating factor at a dose of 5µg/kg per day or at the institutional standard dose) • Cytarabine plus mitoxantrone (CM) for up to four 15–20-day cycles (with cytarabine at a dose of 200mg/m^2 per day on Days 1–7 and mitoxantrone at a dose of 12mg/m^2 per day on Days 1–3; for mitoxantrone, dose reduction to 8mg was allowed based on age, coexisting conditions, and previous anthracycline use) • High dose cytarabine (HIDAC) for up to one 12-dose cycle (at a dose of 3g/m^2 every 12 hours, or a dose of 1.5g/m^2 for patients ≥55 years of age) Patients who achieved CR could undergo HSCT at the investigator's discretion. (However, some patients progressed to HSCT with CRi, and a small number of patients [8 vs 12 for inotuzumab vs SoC, respectively] received HSCT without either CR or CRi).
Permitted and disallowed concomitant medication	**Permitted concomitant medication:** • Any medication for a concurrent medical condition was permitted and was supplied by the study site. The use of hydroxyurea was permitted for temporary control of WBC elevations in patients with aggressive disease both prior to and during the first 5 days of study treatment. Reduction of peripheral blast counts to at least 10,000/µL was required for randomisation. If required, hydroxyurea was given at a dose of 1–5g daily for up to 5 days in Cycle 1. • Concurrent therapy for CNS prophylaxis/treatment (e.g. intrathecal methotrexate) was strongly encouraged. • Growth factors such as G-CSF, including pegfilgrastim, and granulocyte-macrophage-colony stimulating factor were allowed as supportive care with each cycle if clinically indicated after the last dose of study drug or chemotherapy in accordance with local guidelines and medical practice. • Corticosteroids were allowed for cytoreduction, CNS prophylaxis/treatment, as premedications for up to 1 day, to treat hypersensitivity reactions for up to 1 day, and as an antiemetic for up to 8 days/cycle as supportive care. Intranasal, inhaled, or topical corticosteroids (i.e. local administration rather than systemic delivery) were allowed, as were low doses of corticosteroids (≤10mg of prednisone or equivalent/day) throughout study participation. Higher doses of steroids were discouraged if alternative therapy was available. It was crucial to enter dosing details for systemic corticosteroids administered in the case report form due to their possible influence on the primary endpoint. **Prohibited concomitant medication:** • Craniospinal radiation therapy (CSXRT) was prohibited during study treatment. If CSXRT was clinically indicated, the patient was withdrawn from study therapy (i.e. EOT). • Anticancer therapy other than as defined/allowed in the protocol and other investigational agents were prohibited throughout the treatment period of the study. • Medications known to predispose patients to Torsades de pointes were prohibited throughout the treatment period of the study.

Study	INO-VATE 1022
	If a medication known to predispose to Torsades de pointes was considered medically necessary to treat a life-threatening condition, the Sponsor was to be notified immediately, and additional ECGs may have been required prior to redosing with study drug. **Discouraged concomitant medication:** • Patients were strongly encouraged to avoid agents known to be strong cytochrome P450 (CYP) -inducing or -inhibiting agents for the duration of the treatment period of the study. However, these medications were permitted if clinically indicated and necessary. In addition, patients were strongly encouraged to avoid herbal supplements including, but not limited to, St. John's wort throughout the treatment period of the study. Note: Data not available at the time of the original protocol have indicated that multiple metabolic pathways are involved in the metabolism of unconjugated calicheamicin; and the use of CYP inducing or inhibiting agents is not considered to have a clinically meaningful impact on the pharmacokinetics of inotuzumab.
Primary outcome	The two primary outcomes were: • Complete remission (CR), including complete remission with incomplete haematologic recovery (CRi) was assessed by the EAC at screening, Days 16–28 of Cycles 1, 2 and 3 and then every 1–2 cycles (or as clinically indicated) and at the final visit. Note that the cycle length could be extended from 21 to 28 days to allow for toxicity recovery, if necessary. o CR was defined as a disappearance of leukaemia as indicated by <5% marrow blasts and the absence of peripheral blood leukaemic blasts, with recovery of haematopoiesis defined by an absolut neutrophil count (ANC) ≥1000/µL, platelets ≥100,000/µL, and resolution of any extramedullary disease o CRi was defined as CR except with ANC <1000/µL and/or platelets <100,000/µL • Overall survival (OS), defined as the time from randomisation to the date of death due to any cause (patients for whom the date of death could not be verified were censored at the date of last contact). For the long-term follow-up, patients who discontinued treatment but had not relapsed were followed-up every 12 weeks in Year 1 and 24 weeks in Year 2 (and beyond) for disease assessment. After disease progression, patients were followed up every 12 weeks for survival. The trial is planned to end upon last patient enrolled having been followed for 2 years from randomisation.
RMST analysis of OS	Since the OS data in the study appeared to depart from the proportional hazards assumption, as reflected in the widened separation of the survival curves around 15 months from randomisation (See Section 4.7), an exploratory post-hoc analysis based on the RMST method was conducted. The RMST method is an alternative approach to estimate the treatment effect, especially when the assumption of proportional hazards is not satisfied.[4-6] This method measures the average survival from time 0 to a specified time point (known as the 'truncation time'). As reported by Trinquart et al.[118], in general, RMST-based measures yield more conservative estimates than hazard ratios (HRs), with HRs providing, on average, larger treatment effect estimates than the ratio of RMST; and RMST-based measures should be routinely reported in randomised studies with time-to-event outcomes. The RMST method is discussed in more detail in Section 4.4.

Study	INO-VATE 1022
Major secondary outcomes	Secondary endpoints included: • Progression-free survival (PFS), defined as the time from date of randomisation to the earliest date of the following events: death, progressive disease (objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status), or starting a new induction therapy or post-therapy HSCT without achieving CR/CRi • Minimal residual disease (MRD), defined as the percentage of patients, among those who achieved complete remission (as assessed by the EAC), who had results below the threshold for MRD; specified as 0.01% bone marrow blasts, was assessed by a central laboratory • Duration of remission (CR and CRi), as assessed by the investigator • The rate of subsequent HSCT (patients who achieved response and found a suitable donor could receive HSCT at the investigator's discretion) For the long-term follow-up, patients who discontinued treatment but had not relapsed were followed-up for these outcomes every 12 weeks in Year 1 and 24 weeks in Year 2 for disease assessment. After disease progression, patients were followed up every 12 weeks for survival. • Patient-reported outcomes (assessed at day one of each cycle and at the end of treatment): o EORTC QLQ-C30 o EQ-5D
Other outcomes	• Safety • The relationship between efficacy and the percentage of CD22 positive leukaemic blasts • Pharmacokinetics and pharmacodynamics • Pharmacogenomics • Cytogenetics • Immunogenicity
Pre-planned subgroups	Pre-planned subgroups for analysis of CR/CRi included stratification factors: • Duration of first remission (<12 months or ≥12 months) • Salvage status (first or second) • Age at randomisation (<55 years or ≥55 years) Pre-planned subgroups for analysis of OS included: • Stratification factors (the same as for CR/CRi subgroup analysis) • By salvage status per CRF

Study	INO-VATE 1022
	• By age per CRF (<55 years, ≥55 and <65 years or ≥65 years) • By cytogenetics per local laboratory: diploid (normal), Ph+, t(4;11), and complex • By HSCT prior to enrolment: yes or no • By baseline marrow blast (%): <50% or ≥50% • By baseline peripheral blasts per local laboratory: 0/µL, >0–1000/µL or >1000/µL • By percentage of leukaemic blasts that were CD22-positive at baseline per central laboratory • By type of remission per EAC: CR or CRi in the ITT218 Population • By type of remission per Investigator's assessment: CR or CRi • By MRD status (central review): positive or negative • By post randomisation HSCT: yes or no • By region • By gender • By race • By body mass index (BMI) (<30, ≥30) Pre-planned subgroups for analysis of PFS included: • Stratification factors • Duration of first remission • Salvage status per CRF • Age per CRF (<55 years, ≥55 and <65 years or ≥65 years) • Cytogenetics per local laboratory: diploid (normal), Ph+, t(4;11), and complex
Key: ALL, acute lymphoblastic leukaemia; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CR, complete remission; CRF, case report form; CRi, complete remission with incomplete haematologic recovery; EAC, endpoint adjudication committee; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; EQ-5D, EuroQoL 5 Dimension questionnaire; G-CSF, granulocyte colony-stimulating factor; HSCT, haematopoietic stem cell transplantation; ICD, Informed Consent Document; InO, inotuzumab ozogamicin; ITT, intent-to-treat; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome positive; RMST, restricted mean survival time. **Source:** INO-VATE 1022 CSR[3]	

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Table 12 presents a summary of the hypothesis testing and associated statistical analyses used in the INO-VATE 1022 trial.

As pre-specified in the protocol, the final analysis for CR/CRi was to be performed after the first 218 patients had been followed for at least 3 months after randomisation. The 218th patient was randomised to the study on 26 June 2014. A clinical study report (CSR) (as of cut-off date 2 October 2014) presented efficacy findings, including haematological remission (CR/CRi), DoR, MRD, and HSCT, from the initial 218 patients randomised (ITT218) and patient-reported outcomes (PROs) from all randomised patients by the cut-off date (n=279) and safety findings among all randomised and treated patients (n=259).

The last patient was randomised on 4 January 2015, with 326 patients in total then randomised to the study. As pre-specified in the protocol, the final analysis for OS was to be performed after at least 248 events had occurred. On 8 March 2016, the pre-specified number of events required for final analysis of OS was reached, based on the intent-to-treat (ITT) population. Therefore, this date was selected as the database cut-off date for the final OS analysis, with 252 OS events observed. Progression-free survival (PFS) was analysed at the same time.

Evidence in this submission is presented from this most recent data-cut (8 March 2016), which includes final OS and PFS results, along with updated CR/CRi (per investigator assessment) and DoR for both the original ITT218 population and the overall ITT population. Also presented from this latest data cut are MRD, HSCT, and PROs for the overall ITT population and safety data for all treated patients (the safety population). OS was also analysed using post-hoc restricted mean survival time (RMST) methods, as the OS data in the study appeared to deviate from the proportional hazards assumption routinely used for hazard ratio (HR) estimates around 15 months, and the separation in the survival Kaplan–Meier plots appears after the median had been reached (See Section 4.7). Hence, as the hazard ratio for OS and the median point estimates may not be meaningful, an alternative outcome was investigated to best reflect the data. This is discussed in more detail below.

Analyses suitable for categorical data (e.g. chi-square test or Cochran-Mantel-Haenszel [CMH] chi-square test, as appropriate) were used to compare the proportion of patients achieving selected endpoints (e.g. CR/CRi). In cases of rare events, Fisher's exact test was used for treatment comparisons. Treatment groups were compared at the 1-sided 0.0125 significance level, and 95% confidence intervals were presented, except for OS where the HR and corresponding 97.5% 2-sided CI using stratified Cox proportional hazard regression (using the same stratification factors as for randomisation) are presented, alongside p-values.

There were more patients in the control arm than the inotuzumab arm who dropped out prior to receiving treatment (19 vs 0, respectively). To take this into account, sensitivity analyses were performed, assuming that those patients who refused treatment were responders, which is considered to be a very conservative assumption (in favour of the control arm).

In the OS analyses, patients were not censored based on receiving subsequent therapies. For the analyses of PFS, starting a new induction therapy or moving to post-induction HSCT without achieving CR/CRi were classed as progression events.

For the duration of remission (DoR) analyses, patients were not specifically censored for HSCT. However, when they progressed to receive HSCT no further bone marrow samples were collected from them, effectively removing them from the analyses. Therefore, there would have been patients receiving HSCT and still in remission who would not have been included in the analysis, shortening the reported DoR. In addition, only patients who achieved CR/CRi were included in the analyses. [redacted] the definition of DoR was extended to include all patients in the ITT (and the ITT218) populations, with non-responders being given a duration of remission of zero. [redacted]

To address censored patients within the INO-VATE 1022 trial, alternative statistical analyses were conducted to determine which deaths were due to causes other than R/R B-cell ALL. Death due to other causes were considered "competing risks", resulting in the use of two common approaches for conducting competing risk analyses. One approach models the cause-specific hazard of each event separately, by applying the standard Cox regression for the event of interest and censoring all

other observations including confounding risk events, which can lead to biased estimation unless it can assume that competing risks are independent. Censoring patients in the survival analyses of the INO-VATE 1022 trial was done to establish the impact of competing risks (i.e. treatment with subsequent therapies and HSCT date/status). These were considered independent risks, meaning that the survival analyses were not susceptible to statistical bias.

RMST methods for OS analysis

In the presence of proportional hazards, a hazard ratio (HR) calculated over the full observed period of a study (the global HR) has a clear interpretation as a measure of relative efficacy. It can appropriately be interpreted as a summary statistic that represents average treatment effect over the duration of the trial. Because HR on its own cannot indicate absolute treatment benefit, median survival time is typically used alongside HR to provide context of absolute risk and treatment benefit. However, median survival estimates only capture the experience of the first 50% of the population to die and may not be reflective of the profile of longer term survival if that profile changes over time.

When there are clear and obvious departures from proportional hazards, the difference in median survival between arms is likely to be a poor representation of treatment benefit over the full period, therefore alternative methods that use the entirety of the data to summarise the relative treatment benefits are appropriate.[119, 120]

The RMST method is an alternative summary measure of observed survival experience. RMST is the mean survival time from randomization to a clinically relevant time horizon (t*) equivalent to the area under the Kaplan–Meier curve up to the specified time.[4] When calculated over an appropriate follow-up time, ratio of RMST provides a single measure that captures the treatment effect up to that specified time point.[6] RMST difference can be considered as a complementary method to HR and median survival for summarising treatment effects over the duration of a clinical study, particularly when the assumption of proportional hazards does not apply.[121]

RMST has been used previously, within the manufacturer's submission of TA359 (idelalisib for treating chronic lymphocytic leukaemia), to demonstrate that "end of

life" criteria were met.[8] RMST has also been presented and accepted within the analysis of comparative clinical benefit in a number of recent NICE submissions in oncology: ramucirumab for previously treated locally advanced or metastatic non-small cell lung cancer (where it was used by the Evidence Review Group) (TA403)[122], pembrolizumab for treating PD-L1-positive non-small cell lung cancer after chemotherapy (TA428, 2017)[7], nivolumab in advanced (unresectable or metastatic) melanoma in adults (TA384)[9 2016] and ipilimumab for adults with previously untreated advanced (unresectable or metastatic) melanoma (TA319).[10 2014]

The default time point for these analyses in the statistical package corresponds to the shorter of the maximum OS time in the two arms of the study, i.e. looking at the last censored event in each arm and taking the shortest, which was at 24 months. These results are presented for consistency. However, the developer of the statistical package recommends that this default timepoint is not used for the analysis, but that a timepoint directly connected to clinical interests or study objectives is used instead.[123] To this end, a timepoint reflecting the maximum observation time from the arms, i.e. 37.7 months, was used to more fully capture the data across the whole trial.

Table 12: Summary of statistical analyses in INO-VATE 1022

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
INO-VATE 1022	The primary objectives of the study were to compare haematological remission rate (CR/CRi), as assessed by the independent external EAC, and OS in patients with relapsed or refractory CD22-positive B-cell ALL randomised to receive inotuzumab or Investigator's choice of chemotherapy.	Final analysis of haematologic remission (CR/CRi), DoR, and MRD was to be performed after the first 218 randomised patients had been followed for at least 3 months after randomisation. The primary endpoint of OS was planned to be analysed at 2 interim analyses and final analysis. The 2 planned interim analyses were conducted when approximately 25% and at least 60% of the required OS events were reached (for futility [first interim analyses], and efficacy and futility [second interim analyses]). The final analysis for OS was planned to occur after at least 248 OS events were reported. Interim OS analysis results remained confidential to the eDMC until final OS analysis was conducted. The primary population for the final analysis was the ITT218 for CR/CRi (a subset of the ITT population that included the first 218 randomised patients) and ITT for OS. CR/CRi rates were compared between the inotuzumab arm and the control arm using the Chi-square test or Fisher's exact test (if any cell size was under 5) at 1-sided α=0.0125 significance level. For	The sample size was calculated to allow adequate independent assessments of between-group differences in the rate of complete remission and in OS by splitting the one-sided alpha level of 0.025 evenly between the two primary end points. It was calculated that a sample size of 218 patients would give the trial at least 88.5% power to detect a difference in the rate of complete remission (including complete remission with incomplete haematologic recovery) of 24 percentage points between the two groups (61% in the inotuzumab group vs 37% in the standard-therapy group), at a one-sided alpha level of 0.0125. It was also calculated that accrual of at least 325 patients and 248 OS events would give the trial 80% power to detect an increase in OS of at least 50% (median increase, 6.45 months in the inotuzumab group and 4.30 months in the standard care group; hazard ratio, 0.67), at a one-sided alpha level of 0.0125. All reported P values are two-sided.	Tumour assessments were performed by Investigators and by EAC. Independent reviewers were blinded to treatment allocation and Investigator's assessment. An eDMC was responsible for the ongoing monitoring of the efficacy and safety of patients in this study. A HEAB, blinded to study treatment, reviewed safety data with respect to particular hepatic events (e.g. potential cases of VOD) and provided adjudication of the event, which was shared with the eDMC. An independent EAC reviewed the primary efficacy assessments for CR/CRi in the ITT218. For the time to event endpoints, the primary missing data handling method was censoring. For the OS analysis, only death was considered as an event. Patients who withdrew or were lost to follow-up without death were censored at the last date known to be alive. Patients were not censored on receiving subsequent therapy. For PFS analysis, PFS time was measured from date of randomisation to date of first PFS event, defined as death, progressive disease (objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status) or starting new induction therapy or post-therapy HSCT without achieving CR/CRi. Patients who did not have an event by time

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		each treatment arm, the CR/CRi rate along with the 95% CI around the rate was computed. The OS of patients randomised to the inotuzumab arm was compared to that of the control arm using the stratified log-rank test at a 1-sided 0.0125 significance level. The HR and corresponding 97.5% 2-sided CI using stratified Cox proportional hazard regression (same stratification factors as for randomisation) is presented. The median OS was estimated using the Kaplan–Meier method and is reported with 2-sided 95% CIs for each arm. OS was also analysed using RMST methods, as the OS data in the study appeared to deviate from the proportional hazards assumption routinely used for HR estimates around 15 months, and therefore may not be meaningful.		of analysis were censored at the date of last valid tumour assessment. Valid tumour assessment was defined as a tumour assessment with overall time point response of CR/CRi, PR, resistant disease, death during aplasia, relapse from CR/CRi or PD, but not indeterminate or unevaluable. For a patient who had an event more than 28 weeks after the last tumour assessment, the patient was censored at the last tumour assessment date for primary analysis. Patients with no baseline tumour assessment were censored at the randomisation date.

Key: ALL, acute lymphoblastic leukaemia; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; DoR, duration of remission; EAC, endpoint adjudication committee; eDMC, external Data Monitoring Committee; HEAB, Hepatic Events Adjudication Board; ITT, intent-to-treat; ITT218, intent-to-treat analysis on the first 218 randomised patients; MRD, minimal residual disease; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; RMST, restricted mean survival time; VOD, veno-occlusive liver disease.
Source: INO-VATE 1022 CSR[3]

4.5 Participant flow in the relevant randomised controlled trials

4.5.1. Patient disposition

The ITT population included all 326 patients randomised in the study. A summary of the population included in the trial is presented in Table 13.

In the ITT population, all patients in the inotuzumab arm received treatment compared to 88.3% (143 patients) in the control arm. Sensitivity analyses to capture this difference (See Section 4.4) show results that were consistent with the overall analysis.

A total of 6.1% in the inotuzumab arm compared to 0.6% in the control arm (10 vs 1 patient, respectively) completed the maximum number of cycles of treatment allowed by the protocol (up to 6 cycles of inotuzumab and up to 4 cycles of the investigator's choice of chemotherapy, or 2 cycles of 12 doses of HIDAC). The median number of treatment cycles started was three in the inotuzumab group, compared to only one in the control group.

In the ITT population, 76.2% of patients in the inotuzumab arm and 90.7% of patients in the control arm permanently discontinued from the study. The most common reason for discontinuation from the study was patient death (inotuzumab = 74.4%; control = 79.6%). One (0.6%) patient refused further follow-up in the inotuzumab arm, compared to 16 (9.9%) patients in the control arm.

As of the database cut-off date of 8 March 2016, 54 out of 307 treated patients were still in follow-up on study, including 39 patients in the inotuzumab arm, and 15 patients in the control arm.

Table 13: Summary of patient evaluation groups

Number (%) of patients	Inotuzumab	SoC	Total
All patients	**164**	**162**	**326**
Randomised (as of 8 March 2016)	164	162	326
Treated	164 (100.0)	143 (88.3)	307 (94.2)
• Completed treatment[a]	10 (6.1)	1 (0.6)	11 (3.4)
• Completed study[b]	0	0	0
• Discontinued	125 (76.2)	128 (79.0)	253 (77.6)

Number (%) of patients	Inotuzumab	SoC	Total
study[c]			
• Ongoing at cut-off[d]	39 (23.8)	15 (9.3)	54 (16.6)
Analysed for safety[e]	164	143	307
• Adverse events[f]	163 (99.4)	143 (88.3)	306 (93.9)
• Laboratory data	164 (100.0)	143 (88.3)	307 (94.2)

Key: ITT, intent-to-treat; SoC, standard of care.
Notes: [a] Patients that received the maximum number of cycles and doses allowed per protocol; [b] Completed survival follow-up for 5 years from randomisation or 2 years from randomisation of the last patient; [c] Included all discontinuation reasons, including death, lost to follow-up, withdrawal by patient, other, except completed study; [d] Patients who had not discontinued study or completed the study; [e] Analysis for safety included all randomised patients who received at least one dose of a test article (either inotuzumab or defined Investigator's choice of chemotherapy); [f] Included patients with any adverse event.
Source: INO-VATE 1022 CSR[3]

4.5.2. Baseline characteristics

Table 14 presents the baseline characteristics for the both ITT218 remission analysis population (i.e., the ITT analysis of the first 218 randomised patients, which was the primary population for the CR/CRi analysis, as specified in the protocol) and the overall ITT population.

Given that R/R B-cell ALL is such a rare condition, it is difficult to specify a standard patient population. In a recent advisory board with UK clinical experts, some clinicians thought that the population in the INO-VATE 1022 trial was younger than would be expected in UK clinical practice, whereas others thought that the trial population was similar to what they would expect.[48] For comparison, in an RCT in this population for another treatment currently being assessed (the TOWER study for blinatunumab)[98] the median age of patients is 37, which is even younger than the population in the INO-VATE trial. As these patients were required to be fit for intensive therapy (and therefore able to progress to HSCT, if possible) it is considered that the population of the INO-VATE 1022 trial is consistent with what would be expected in a UK patient population.

Table 14: Baseline characteristics of INO-VATE 1022

	ITT218 population[a]		ITT population	
	Inotuzumab (N = 109)	**SoC (N = 109)**	**Inotuzumab (N = 164)**	**SoC (N = 162)**
Age, mean (SD)	NR	NR	45.9 (17.1)	46.0 (16.6)
Age, median (range)	47 (18.78)	47 (18–79)	46.5 (18–78)	47.5 (18–79)
Male, n (%)	61 (56)	73 (67)	91 (55.5)	102 (63.0)
Race[b], white, n (%)	76 (70)	79 (72)	112 (68.3)	120 (74.1)
ECOG PS, n (%)[c]				
• 0	43 (39)	45 (41)	62 (37.8)	61 (37.7)
• 1	50 (46)	53 (49)	81 (49.4)	80 (49.4)
• 2	15 (14)	10 (9)	21 (12.8)	20 (12.3)
• Missing data	1 (1)	1 (1)	0	1 (0.6)
Salvage-treatment phase, n (%)				
• First	73 (67)	69 (63)	111 (67.7)	104 (64.2)
• Second	35 (32)	39 (36)	51 (31.1)	57 (35.2)
• Missing data	1 (1)	1 (1)	2 (1.2)[d]	1 (0.6)[d]
Duration of first remission, n (%)				
• <12 months	62 (57)	71 (65)	98 (59.8)	108 (66.7)
• ≥12 months	47 (43)	38 (35)	66 (40.2)	54 (33.3)
Previous HSCT, n (%)	17 (16)	22 (20)	28 (17)	26 (18)
Number of previous induction therapies, n (%)				
• 1	75 (69)	69 (63)	112 (68.3)	104 (64.2)
• 2	33 (30)	39 (36)	50 (30.5)	57 (35.2)
• 3	1 (1)	1 (1)	2 (1.2)	1 (0.6)
Response to most recent previous induction therapy, n (%)				
• Complete response	78 (72)	74 (68)	121 (73.8)	111 (68.5)
• Partial response	9 (8)	7 (6)	11 (6.7)	10 (6.2)
• Treatment-resistant disease	17 (16)	18 (17)	28 (17.1)	30 (18.5)
• Progressive or stable disease	4 (4)	10 (9)	4 (2.4)	10 (6.2)

	ITT218 population[a]		ITT population	
	Inotuzumab (N = 109)	**SoC (N = 109)**	**Inotuzumab (N = 164)**	**SoC (N = 162)**
White cell count, per mm^3, median (range)	3,500 (0–47,400)	3,800 (100–51,000)	4,100 (0–47,400)	4,000 (100–68,800)
Peripheral blast count, per mm^3, median (range)[e]	175.4 (0–42,660)	39.3 (0–31,500)	107.6 (0–42,660)	30.0 (0–43,331.4)
• Missing data, n (%)	1 (1)	1 (1)	1 (0.6)	3 (1.9)
No circulating peripheral blasts, n (%)	42 (39)	48 (44)	71 (43.3)	74 (45.7)
Bone marrow blasts, n (%)				
• <50%	30 (28)	29 (27)	53 (32.3)	48 (29.6)
• ≥50%	77 (71)	78 (72)	109 (66.5)	113 (69.8)
• Missing data	2 (2)	2 (2)	2 (1.2)	1 (0.6)
CD22 expression, n (%)[f]				
• <90%	24 (22)	24 (22)	35 (21.3)	36 (22.2)
• ≥90%	74 (68)	63 (58)	107 (65.2)	93 (57.4)
• Missing data	11 (10)	22 (20)	22 (13.4)	33 (20.4)
Karyotype, n (%)[g]				
• Normal[h]	27 (25)	23 (21)	46 (28.0)	42 (25.9)
• Ph-positive	14 (13)	18 (17)	22 (13.4)	28 (17.3)
• T(4;11)-positive	3 (3)	6 (6)	6 (3.7)	7 (4.3)
• Other abnormalities	49 (45)	46 (42)	70 (42.7)	67 (38.9)
• Unknown or missing data	16 (15)	16 (15)	20 (12.2)	22 (13.6)

Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HSCT, haematopoietic stem cell transplantation; NR, not reported; Ph, Philadelphia chromosome; SoC, standard-of-care.
Notes: [a] The remission-analysis population includes the first 218 patients who underwent randomisation in the intent-to-treat population; [b] Data on race were provided by the trial centre; [c] ECOG PS scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing symptoms; [d] Includes salvage 3 up or missing; [e] The peripheral-blast count is the product of the number of peripheral blasts multiplied by 0.01 and the number of white cells multiplied by 1000; [f] CD22 expression was assessed at a central laboratory; [g] Karyotype was assessed at a local laboratory, although Philadelphia chromosome (Ph) positivity could be assessed at a central laboratory or local laboratory or through medical history; [h] The assessment of normal karyotype was based on a minimum of 20 metaphases.
Source: INO-VATE 1022 CSR[3]

4.5.3. Subsequent induction therapies

Table 15 presents a list of the subsequent induction therapies used by patients in each treatment arm in the INO-VATE 1022 study.

The cohort in the inotuzumab arm used fewer subsequent induction therapies than the control arm. This may be the result of more inotuzumab patients achieving remission and going on to subsequent HSCT (thus less need for subsequent salvage). Of note, there was a marked increase in the use of blinatumomab, chemotherapy, TKIs and steroids in the control arm.

Table 15: Subsequent induction therapies used in the INO-VATE 1022 trial (ITT population)

Follow-up systemic induction therapy, n (%)	Inotuzumab (N = 164)	SoC (N = 162)
[redacted]	[redacted]	[redacted]

Source: INO-VATE 1022 CSR[3]

4.6 Quality assessment of the relevant randomised controlled trials

The INO-VATE 1022 trial was conducted in accordance with good clinical practice (GCP) guidelines, using a single protocol to promote consistency across sites, and with measures taken to minimise bias.

Quality assessment in accordance with the NICE recommended checklist for RCT assessment of bias is presented in Table 16. The overall risk of bias for the INO-VATE 1022 trial is deemed low.

For ethical reasons, the INO-VATE 1022 trial was not blinded and patients had the right to withdraw from the study at their own discretion. The potential issue as a result of this was that more patients in the control arm were not treated following randomisation, due to withdrawn consent, possibly due to patients choosing to join a trial in the hope of receiving a new therapy option that is more effective than the SoC, and then deciding to withdraw once they received their treatment allocation. However, sensitivity analyses of the results to account for this by removing these patients (described in Section 4.4) supported the overall findings of the trial with respect to inotuzumab's comparative benefit.

As set out in Section 4.5.2 it is considered that the population of the INO-VATE 1022 trial is consistent with what would be expected in UK practice.[48]

Overall, consulted experts agreed the trial was sufficiently reflective of routine clinical practice in England and Wales. Inotuzumab is expected to be licensed for use in both Ph- and Ph+ patients, and therefore treatment within the INO-VATE 1022 trial was irrespective of Ph-positivity. Clinicians agreed that the choice of comparator reflected the most commonly used treatment for R/R B-cell ALL patients[48], and treatments were administered and outcomes assessed in line with standard practice.

Table 16: Quality assessment results for INO-VATE

Study question	**How is the question addressed in the study?**		**Risk of bias**
Was randomisation carried out appropriately?	Yes	Patients were randomised using randomly permuted blocks with stratification for key prognostic factors.	Low
Was the concealment of treatment allocation adequate?	Yes	Randomisation implemented via a centralised IVRS.	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Patient demographics were well balanced, with no key differences between treatment groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	This was an open-label study. However, to minimise bias, the study was conducted as a blinded study in regards to cumulative efficacy and comparative safety	Low

Study question	How is the question addressed in the study?		Risk of bias
		results to all study personnel, as well as the eDMC, EAC and HEAB for outcome assessments. Also, the co-primary endpoint of OS is not a subjective outcome.	
Were there any unexpected imbalances in drop-outs between groups?	Yes	More patients in the control arm were not treated following randomisation, due to withdrawn consent (possibly due to the open-label nature of the trial). However, sensitivity analyses of the results to account for this supported the overall findings of the trial.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Primary analyses for CR/CRi were on the ITT218 population, i.e. the ITT population for the first 218 randomised patients. But overall ITT analyses were also performed and results were consistent. Primary analyses for OS were on the ITT population. Standard censoring methods were used to account for missing data.	Low

Key: EAC, endpoint adjudication committee; eDMC, external Data Monitoring Committee; HEAB, Hepatic Events Adjudication Board; ITT, intent-to-treat; IVRS, interactive voice response system.
Source: INO-VATE 1022 CSR[3]

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Primary endpoints in INO-VATE 1022

CR/CRi (ITT218 population, primary analysis)

CR/CRi outcomes in the ITT218 population, as assessed by the endpoint adjudication committee (EAC) (the primary analysis for CR/CRi outcomes) are presented in Table 17.

The CR/CRi rate (per EAC), was 80.7% (95% CI: 72.1, 87.7) in the inotuzumab arm compared to 29.4% (95% CI: 21.0–38.8) in the control arm. The rate difference was

51.4% (97.5% CI: 38.4, 64.3) and was statistically significant (1-sided p<0.0001 [Chi-square test]).

The CR rate (per EAC) was 35.8% (95% CI: 26.8–45.5) in the inotuzumab arm compared to 17.4% (95% CI: 10.8, 25.9) in the control arm. The rate difference was 18.3% (97.5% CI: 5.2, 31.5) and was statistically significant (1-sided p=0.002 [Chi-square test]).

The CRi rate (per EAC) was 45.0% (95% CI: 35.4, 54.8) in the inotuzumab arm compared to 11.9% (95% CI: 6.5, 19.5) in the control arm. The rate difference was 33.0% (97.5% CI: 20.3, 45.8) and was statistically significant (1-sided p<0.0001 [Chi-square test]).

Table 17: INO-VATE 1022 remission outcomes (ITT218 population)

	Inotuzumab (N = 109)	**SoC (N = 109)**	**Rate difference**	**p-value**
CR/CRi, n (%)	88 (80.7)	32 (29.4)	51.4	<0.0001
95% CI for rate; 97.5% CI for rate difference	72.1, 87.7	21.0, 38.8	38.4, 64.3	
CR, n (%)	39 (35.8)	19 (17.4)	18.3	0.002
95% CI for rate; 97.5% CI for rate difference	26.8, 45.5	10.8, 25.9	5.2. 31.5	
CRi, n (%)	49 (45.0)	13 (11.9)	33.0	<0.0001
95% CI for rate; 97.5% CI for rate difference	35.4, 54.8	6.5, 19.5	20.3, 45.8	
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; SoC, standard of care. **Source:** INO-VATE 1022 CSR[3]				

CR/CRi (ITT population)

The CR/CRi findings in the ITT population were consistent with the results from the ITT218 population (Table 18).

The CR/CRi rate was [redacted] (95% CI: [redacted]) in the inotuzumab arm compared to [redacted]% (95% CI: [redacted]) in the control arm. The rate difference was [redacted](97.5% CI: [redacted]) and was statistically significant (1-sided p[redacted] [Chi-square test]).

The CR rate was [redacted](95% CI: [redacted]) in the inotuzumab arm compared to [redacted]% (95% CI: [redacted]) in the control arm. The rate difference was [redacted]% (97.5% CI: [redacted]) and was statistically significant (1-sided p=[redacted] [Chi-square test]).

The CRi rate was [redacted]% (95% CI: [redacted]) in the inotuzumab arm compared to [redacted]% (95% CI: [redacted]) in the control arm. The rate difference was [redacted]% (97.5% CI: [redacted]) and was statistically significant (1-sided p[redacted][Chi-square test]).

Table 18: INO-VATE 1022 remission outcomes (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**	**Rate difference**	**p-value**
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	
CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	
CR/CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

Pre-specified overall survival (ITT population)

The OS outcomes in the ITT population are presented in Table 19. The estimated HR (inotuzumab vs the control arm) was 0.77 (97.5% CI: 0.58, 1.03; 1-sided p=0.0203) based on the stratified analysis, suggesting a 23% reduction in the risk of death in favour of inotuzumab. The estimated HR (inotuzumab vs control arm) was [redacted] (97.5% CI: [redacted]) based on the unstratified analysis, indicating an overall [redacted]% reduction in the risk of death in favour of inotuzumab. Although this median result did not meet the pre-specified p-value, [redacted] a 1-sided test (0.025) for OS can be considered. This renders the improvement in OS associated with inotuzumab over control to be statistically significant.

The Kaplan–Meier plot (Figure 8) indicated that the difference in survival between the two arms varied according to the time from randomisation, and therefore, proportional hazards are not observed for these data. As such, the HR should be interpreted with caution due to non-proportional hazards, as discussed in Section 4.4.

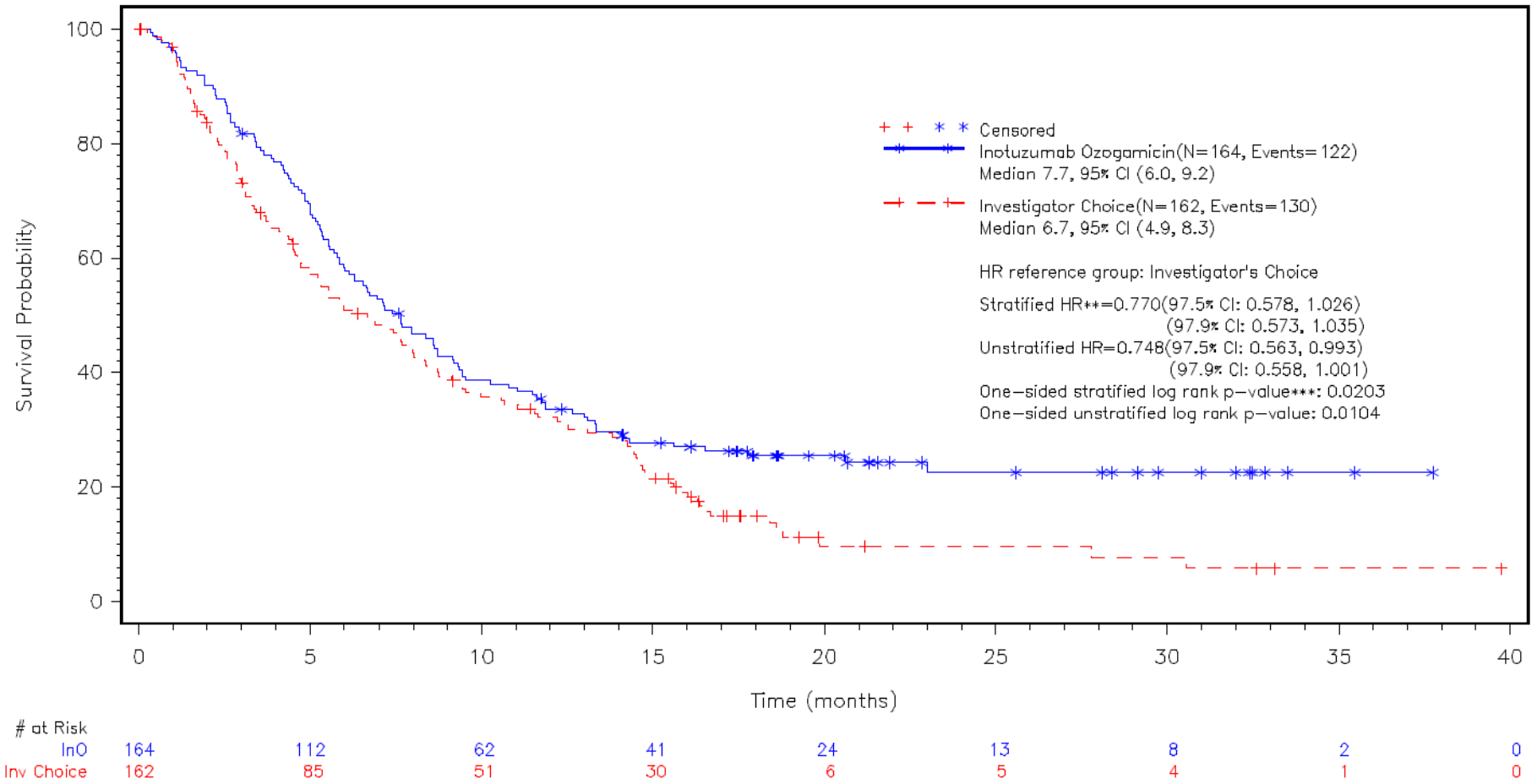
The median OS was 7.7 months (95% CI: 6.0–9.2) in the inotuzumab arm compared to 6.7 months (95% CI: 4.9–8.3) in the control arm. Again, as the HR is not constant (*i.e.* non-proportional) and a comparison of the medians is not reflective of the whole survival distribution due to the separation in the tails of the curves, these results should be interpreted with caution. For example, the survival probability at 6 months was [redacted]) in the inotuzumab arm compared to [redacted]) in the control arm, at 12 months was [redacted]) in the inotuzumab arm compared to [redacted]) in the control arm, and at 24 months was [redacted]) in the inotuzumab arm compared to [redacted]) in the control arm. Further, by observing Figure 8 can be seen that the curves continue to separate past 24 months.

Table 19: INO-VATE 1022 OS outcomes (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**	**p-value**
OS			
Median, months (95% CI)	7.7 (6.0, 9.2)	6.7 (4.9, 8.3)	
Number of deaths, n (%)	122 (74.4)	130 (80.2)	
Number censored, n (%)	42 (25.6)	32 (19.8)	
Survival probability, % (95% CI)			
• 6-months	[redacted]	[redacted]	
• 12-months	[redacted]	[redacted]	
• 24-months	[redacted]	[redacted]	
HR, stratified (97.5% CI)	0.770 (0.578, 1.026)		0.0203
HR, unstratified (97.5% CI)	0.748 (0.563, 0.993)		0.0104

Key: CI, confidence interval; HR, hazard ratio; OS, overall survival; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

Figure 8: Kaplan–Meier plot of overall survival (ITT population)



Key: # at risk, number at risk; CI, confidence interval; HR, hazard ratio; Inv Choice, investigator's choice of chemotherapy.
Source: INO-VATE 1022 CSR[3]

Restricted mean survival time analysis of overall survival in INO-VATE 1022

Since the OS data in the study depart from the proportional hazards assumption, as evidenced by the widened separation of the survival curves around 15 months from randomisation (Figure 8), an exploratory post-hoc analysis based on the RMST method was conducted. Further details on the RMST methods, the rationale for its use, and examples of previous NICE appraisals where it has been presented, were presented in Table 11 and Section 4.4.

Table 20 presents the OS analysis based on the RMST in the ITT population, using the 37.7-month cut-off (as explained in Section 4.4). The restricted mean OS was 13.9 months (SE: 1.1) in the inotuzumab arm and 9.9 months (SE: 0.9) in the control arm, producing a gain of 3.9 months associated with inotuzumab (95% CI: 1.2–6.7) in a 37.7-month maximum follow-up with a 1-sided p-value of 0.0023.

Table 20: Summary of RMST for OS (ITT population)

	Inotuzumab (N=164)	**SoC (N=162)**	**2-sided p-value**	**1-sided p-value**
Truncation time, tau (months)[a]		37.7	NA	NA
Number of deaths, n (%)	122 (74.4)	130 (80.2)	NA	NA
RMST, months (SE)	13.9 (1.1)	9.9 (0.9)	NA	NA
95% CI	11.7, 16.0	8.3, 11.6	NA	NA
RMTL, months (SE)	23.8 (1.1)	27.8 (0.9)	NA	NA
95% CI	21.7, 26.0	26.1, 29.4	NA	NA
Difference (reference group: SoC)				
RMST difference, months (95% CI)		3.9 (1.2, 6.7)	0.0046	0.0023
RMST ratio, months (95% CI)		1.4 (1.1, 1.8)	0.0042	0.0021
RMTL ratio, months (95% CI)		0.9 (0.8, 1.0)	0.0057	0.0029

Key: CI, confidence interval; ITT, intent-to-treat; NA, not applicable; OS, overall survival; RMST, restricted mean survival time; RMTL, restricted mean time lost; SoC, standard of care.
Notes: [a] Truncation time of 37.7 months was chosen as the minimum of the maximum OS time in the two arms of the study.
Source: INO-VATE 1022 CSR[3]

Results from a 24-month cut-off in the RMST analysis were generally consistent with the 37.7-month analysis. Mean OS was 10.8 months (SE: 0.7) in the inotuzumab arm and 8.9 months (SE: 0.6) in the control arm, resulting in a statistically significant

gain of 1.8 months (95% CI: 0.1–3.6) in 24-month follow-up (p=0.04). However, the gain is greater after 37.7 months than 24 months as the curves further separation with time (observed in Figure 8).

Secondary endpoints in INO-VATE 1022

PFS (ITT population)

A summary of PFS outcomes are presented in Table 21. In the ITT population, the estimated HR (inotuzumab vs the control arm) was 0.45 (97.5% CI: 0.34, 0.61; 1-sided p<0.0001) based on the stratified analysis, and 0.46 (97.5% CI: 0.35, 0.62; 1-sided p<0.0001) based on the unstratified analysis.

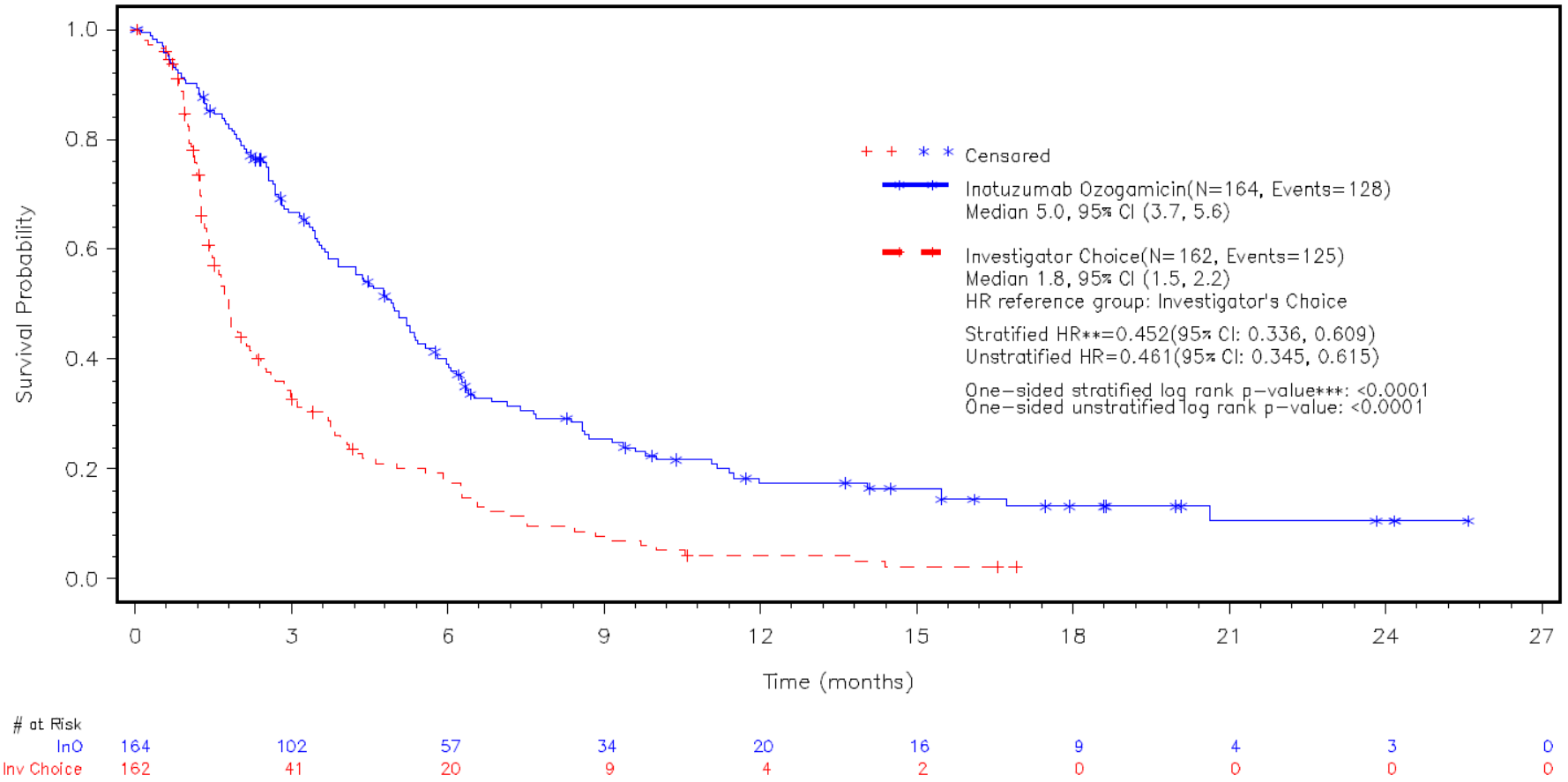
The median PFS was 5.0 months (95% CI: 3.7–5.6) in the inotuzumab arm versus 1.8 months (95% CI: 1.5–2.2) in the control arm. Kaplan–Meier curves of PFS are presented in Figure 9.

Table 21: PFS outcomes in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
Progression-free survival		
Total patients with events, n (%)	128 (78.0)	125 (77.2)
• Death	[redacted]	[redacted]
• Progressive disease		
o Objective progression	[redacted]	[redacted]
o Relapse from CR/CRi	[redacted]	[redacted]
o Treatment discontinuation due to global deterioration of health status	[redacted]	[redacted]
• Starting new induction therapy or post-therapy HSCT without achieving CR or CRi	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	5.0 (3.7, 5.6)	1.8 (1.5, 2.2)
Probability of being event-free at 12-months (95% CI)	[redacted]	[redacted]
Stratified HR (97.5% CI) [p-value]	0.452 (0.336, 0.609) [<0.0001]	
Unstratified HR (97.5% CI) [p-value]	[redacted]	

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; InO, inotuzumab ozogamicin; PFS, progression-free survival; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

Figure 9: Kaplan–Meier plot of progression-free survival (ITT population)



Key: CI, confidence interval; HR, hazard ratio; Inv, investigator; ITT, intent-to-treat; IVRS, Interactive Voice Response System.
Notes: **, From stratified Cox proportional hazards model. The stratification factors were duration of first remission (<12 months or ≥12 months); salvage treatment (Salvage 1 or 2); patient age at randomisation (<55 years or ≥55 years). All factors were per IVRS.
***, From 1-sided stratified log-rank test. The stratification factors were duration of first remission (<12 months or ≥12 months); salvage treatment (Salvage 1 or 2); patient age at randomisation (<55 years or ≥55 years). All factors were per IVRS.
Source: INO-VATE 1022 CSR[3]

Minimal residual disease (ITT population)

As explained in Section 3.1, MRD negativity is an important outcome in R/R B-cell ALL. A summary of MRD outcomes are presented in Table 22. In patients achieving a CR/CRi (per Investigator) in the ITT population, a greater proportion of patients in the inotuzumab arm achieved MRD negativity compared to the control arm.

Among patients who achieved CR/CRi, [redacted]% achieved MRD negativity in the inotuzumab arm and [redacted]% in the control arm (1-sided p<[redacted]) for a rate difference of [redacted]%.

Among patients who achieved CR, [redacted]% achieved MRD negativity in the inotuzumab arm and [redacted]% in the control arm (1-sided p[redacted]).

Among patients who achieved CRi, [redacted]% achieved MRD negativity in the inotuzumab arm and [redacted]% in the control arm (1-sided p=[redacted]).

Table 22: MRD outcomes in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
Minimal residual disease		
Patients with CR/CRi	[redacted]	[redacted]
MRD in patients achieving CR/CRi, n (%) [95% CI]		
• Positive	[redacted]	[redacted]
• Negative	[redacted]	[redacted]
• No post-baseline MRD results	[redacted]	[redacted]
Patients with CR	[redacted]	[redacted]
MRD in patients achieving CR, n (%) [95% CI]		
• Positive	[redacted]	[redacted]
• Negative	[redacted]	[redacted]
• No post-baseline MRD results	[redacted]	[redacted]
Patients with CRi	[redacted]	[redacted]
MRD in patients achieving CRi, n (%) [95% CI]		
• Positive	[redacted]	[redacted]
• Negative	[redacted]	[redacted]
• No post-baseline MRD results	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; MRD, minimal residual disease; PFS, progression-free survival; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

OS outcomes by MRD status

Table 23 presents the OS outcomes by MRD status. OS for patients who achieved MRD-negativity was much [redacted] than for those who did not: [redacted] months for patients who achieved MRD-negativity in the inotuzumab and the control arm, respectively, compared to [redacted] months for those who did not achieve MRD-negativity (same in both arms). This suggests that MRD-negativity is a prognostic factor for longer OS, which has been previously supported in the literature.[45] This is shown in the Kaplan–Meier curve for OS by MRD status in CR/CRi patients treated with inotuzumab, presented in Figure 10.

It is worth noting that there are much smaller numbers of patients who achieved MRD-negativity in the control arm compared to the inotuzumab arm, so these survival outcomes should be interpreted with caution. However, in general, patients who achieve MRD-negativity experience longer survival times, and more patients treated with inotuzumab can achieve MRD negativity.

Table 23: OS outcomes by MRD status (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
MRD-negative, n	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Number of events, n	[redacted]	[redacted]
Stratified HR (97.5% CI) [p-value]	[redacted]	
Unstratified HR (97.5% CI) [p-value]	[redacted]	
MRD-positive, n	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Number of events, n	[redacted]	[redacted]
Stratified HR (97.5% CI) [p-value]	[redacted]	
Unstratified HR (97.5% CI) [p-value]	[redacted]	

Key: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MRD, minimal residual disease; n, number of patients; OS, overall survival; standard of care.
Source: INO-VATE 1022 CSR[3]

[redacted]10[redacted]

Key: CI, confidence interval; HR, hazard ratio; InO, inotuzumab ozogamicin; MRD, minimal residual disease.
Source: INO-VATE 1022 CSR[3]

Subsequent HSCT (ITT population)

More patients in the inotuzumab arm than in the control arm proceeded to HSCT after study therapy and prior to the start of any post induction therapy (e.g., without another intervening induction therapy and regardless of CR/CRi status) (Table 24). In the ITT population, [redacted]% of patients in the inotuzumab arm and [redacted]% of patients in the control arm proceeded to HSCT after study treatment (p<0.0001).

Among these [redacted] patients who received HSCT, [redacted]% were recipients of an allogeneic HSCT ([redacted]% in the inotuzumab arm; [redacted]% in the control arm).

The type of conditioning therapy was myeloablative for [redacted]% of patients in the inotuzumab arm and [redacted]% of patients in the control arm, and reduced intensity for [redacted]% in the inotuzumab arm and [redacted]% in the control arm.

Table 24: Subsequent HSCT in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
HSCT rate		
Patients with HSCT, n (%) [95% CI]	[redacted]	[redacted]
• Difference in HSCT rate between the two arms (95% CI) [p-value]	[redacted]	
Type of transplant, n (%)		
• Allogeneic	[redacted]	[redacted]
• Autologous	[redacted]	[redacted]
Type of conditioning therapy, n (%)		
• Myeloablative	[redacted]	[redacted]
• Reduced intensity	[redacted]	[redacted]

Key: CI, confidence interval; HSCT, haematopoietic stem cell transplantation; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

OS outcomes by subsequent HSCT

Patients who received HSCT had longer OS than patients who did not, with patients who received HSCT after achieving CR/CRi having the longest median OS in both treatment arms. The benefit of inotuzumab comes through higher rates of CR/CRi, thus allowing more people to bridge to HSCT, which is associated with long-term

improvements in survival. This situation is reflective of what happens in UK clinical practice.

It is worth noting that there are much fewer patients in the control arm than in the inotuzumab arm, so the control arm survival outcomes should be interpreted with caution. Additional caution should be taken in interpretation as the patients who have undergone HSCT in the two trial arms are no longer a randomisation comparison. Further, as the tails of the curves show separation ([redacted]), caution should also be made when comparing the medians.

Inotuzumab patients who achieved CR/CRi and received HSCT (as they would in UK clinical practice) had a much higher 2-year survival probability than patients who did not receive HSCT ([redacted]%), as did SoC patients who achieved CR/CRi and received HSCT ([redacted]).

Although the main survival benefit of treatment with inotuzumab comes from getting more patients to HSCT, there is also a survival benefit for patients receiving inotuzumab who are not able to receive this (e.g. because they are unable to find a suitable donor). This is shown in the survival outcomes where with or without censoring for HSCT, the probability of survival at 24-months is higher in patients treated with inotuzumab than the control arm (22.9% vs 9.6% without censoring for HSCT compared to [redacted]% with censoring for HSCT, respectively).

[redacted]

Source: OS analyses post-HSCT[124]

Duration of remission analyses [redacted]

[redacted] the definition of DoR was extended to include all patients in the ITT (and the ITT218) populations, with non-responders being given a duration of remission of zero. This is the DoR analysis that is [redacted], and is therefore presented here as the main DoR analysis.[125]

The median duration of remission in the ITT218 population was [redacted] for inotuzumab patients versus [redacted] in the control arm, and in the overall ITT population this was [redacted] versus [redacted], respectively. These results are presented in Table 25, and were [redacted].

Table 25: Duration of remission analyses [redacted]

	Inotuzumab	SoC	p-value
Duration of remission, ITT218 population	**N = 109**	**N = 109**	
Median (95% CI), months	[redacted]	[redacted]	
HR, stratified (95% CI)	[redacted]		[redacted]
HR, unstratified (95% CI)	[redacted]		[redacted]
ITT population	**N = 164**	**N = 162**	
Median (95% CI), months	[redacted]	[redacted]	
HR, stratified (95% CI)	[redacted]		[redacted]
HR, unstratified (95% CI)	[redacted]		[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; SD, standard deviation; SoC, standard of care.
Source: INO-VATE analyses [redacted][125]

Figure 12 presents the Kaplan–Meier for the ITT population for the DoR analysis [redacted].

Figure 11: [redacted]

Key: [redacted]; ITT, intent-to-treat; HR, hazard ratio.
Source: INO-VATE analyses [redacted][125]

Duration of remission and time to remission (ITT218 population)

In total, 80.7% of patients achieved CR/CRi in the inotuzumab arm compared to 29.4% in the control arm (Table 26).

The observed HR was [redacted]) with 1-sided stratified log-rank p=0.[redacted], based on the stratified analysis, using the stratification factors at randomisation. The median DoR was [redacted]) in the inotuzumab arm and [redacted]) for patients in the control arm.

However, for the DoR analyses, when patients progressed to receive HSCT no further bone marrow samples were collected from them, effectively removing them from the analyses. Therefore, there would have been patients receiving HSCT and still in remission who would not have been included in the analysis, shortening the reported DoR. In addition, only patients who achieved CR/CRi were included in the pre-specified DoR analyses. Therefore, PFS (alongside the DoR analyses [redacted]) is considered to be a more appropriate indicator of a patient's DoR than DoR as reported above.

For patients who achieved CR/CRi, the median time from randomisation to remission favoured inotuzumab, being [redacted] months (range [redacted] months) for patients in the inotuzumab arm and [redacted] months (range [redacted] months) for patients in the control arm.

Table 26: Duration of remission and time to remission endpoints in INO-VATE 1022 (ITT218 population)

	Inotuzumab (N = 109)	**SoC (N = 109)**
Duration of remission		
Patients with CR/CRi, n (%)	88 (80.7)	32 (29.4)
Remission status		
• Patients with CR/CRi and subsequently progressed or died due to any cause while on study	[redacted]	[redacted]
• Patients with CR/CRi who had not progressed or died while on study	[redacted]	[redacted]
KM estimates of remission duration, months, quartiles (95% CI)		
• 25%	[redacted]	[redacted]
• 50%	[redacted]	[redacted]
• 75%	[redacted]	[redacted]
Stratified HR (95% CI) [p-value]	[redacted]	
Unstratified HR (95% CI) [p-value]	[redacted]	
Time from randomisation to remission first documented on study, months	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; KM, Kaplan–Meier; SD, standard deviation; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

Duration of remission and time to remission (ITT population)

In total, [redacted]% of patients achieved CR/CRi in the inotuzumab arm compared to [redacted]% in the control arm (Table 27). The observed HR was [redacted]) with 1-sided log-rank p=0.0052, based on the stratified analysis using the stratification factors at randomisation. The median DoR was [redacted] months (95% CI: [redacted]) in the inotuzumab arm and [redacted] months (95% CI: [redacted]) for patients in the control arm. However, this analysis faces the same issues described for the ITT218 population, which will have shortened the reported DoR. Therefore, PFS (alongside the DoR analyses [redacted]) is again

considered to be a more appropriate indicator of a patient's DoR, than their reported DoR.

Table 27: Duration of remission and time to remission endpoints in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
Duration of remission		
Patients with CR/CRi, n (%) Remission status • Patients with CR/CRi who subsequently progressed or died due to any cause while on study • Patients with CR/CRi who had not progressed or died while on study	[redacted]	[redacted]
KM estimates of remission duration, months, quartiles (95% CI) • 25% • 50% • 75%	[redacted]	[redacted]
Stratified HR (95% CI) [p-value] Unstratified HR (95% CI) [p-value]	[redacted]	
Time from randomisation to remission first documented on study, months	[redacted]	[redacted]
Mean (SD) Median (range)	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; KM, Kaplan–Meier; SD, standard deviation; SoC, standard of care.
Source: INO-VATE 1022 CSR[3]

Patient-reported outcomes (ITT population)

Baseline PRO scores were generally comparable between the treatment arms, with the exceptions of EORTC QLQ-C30 role functioning and EQ-VAS appearing to be generally better in the control arm, and social and cognitive functioning, financial difficulties, and pain, favouring the inotuzumab arm (Table 28).

Table 28: PRO at baseline in INO-VATE 1022 (ITT population)

Characteristics	Inotuzumab (N = 164)	SoC (N = 162)
	Mean (SE)	Mean (SE)
EORTC QLQ-C30[a]		
Physical functioning	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]
Global health status/QoL	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]
Pain	[redacted]	[redacted]
EQ-5D Index[b]	[redacted]	[redacted]
EQ-VAS[c]	[redacted]	[redacted]

Key: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQoL visual analogue scale; EQ-5D, EuroQoL 5 Dimension questionnaire; ITT, intent-to-treat; QoL, quality of life; SE, standard error; SoC standard of care.
Notes: [a], Higher scores are associated with better health for functional scales and global health status/QoL and worse health for symptom scales.
[b], Higher scores are associated with better health for EQ-5D index.
[c], Higher scores are associated with better health for global health status/QoL.
Source: INO-VATE 1022 CSR[3]

EORTC QLQ-C30

Among questionnaires for which patients completed at least one question, the overall completion rate was [redacted]% for the inotuzumab arm and [redacted]% for the control arm. Among questionnaires for which patients completed all questions, the overall completion rate was [redacted]% for the inotuzumab arm and [redacted]% for the control arm.

Completion rates among patients who completed all questions were [redacted] through Cycle 4 in both treatment arms; however, in the control arm, the number of patients remaining on treatment decreased markedly by Cycle 2 ([redacted]/162 [[redacted]%] patients), with only [redacted]%) patients and [redacted]%) patient remaining by Cycle 3 and Cycle 4, respectively. The completion rate at the end of treatment among patients who completed at least 1 question, although poor for both treatment arms, was lower for the control arm ([redacted]% compared to [redacted]% for the inotuzumab arm).

Table 28 presents EORTC QLQ-C30 overall treatment comparisons for the ITT population using longitudinal mixed-effects models with random intercepts and slopes with treatment, time, treatment-by-time interaction, and baseline scores as covariates.

Quality of life, functioning, and symptoms were generally in favour of patients in the inotuzumab arm over the control arm. Patients receiving inotuzumab were observed to have significantly better appetite, were significantly more [redacted], and experienced significantly less impact on family and social life (estimated mean treatment difference [redacted]). They were also statistically significantly more able to perform strenuous activities, basic living needs, work, other daily activities, hobbies, and other leisure activities (Figure 13). It is also generally accepted that changes in HRQL scores between 5% and 10% are regarded by patients as being clinically significant changes.[15] Global health status/QoL, dyspnoea, and fatigue [redacted]).

There was no dimension that was clinically significantly worse for the inotuzumab arm compared to the control arm.

[redacted]

[redacted]

[redacted]

Key: CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQoL visual analogue scale; EQ-5D, EuroQoL 5 Dimension questionnaire; InO, inotuzumab ozogamicin; SOC, standard of care.
Notes: * p<0.05; † 95% CI error bar (-0.01 to 0.07) within the symbol.
Estimated means were least squares means of each domain's post-baseline scores, estimated from repeated measures mixed effects model with treatment, time, treatment-by-time interaction, and baseline scores as covariates.
Source: Kantarjian (2016) ASH Poster[111]

EQ-5D

Completion rates for the EQ-5D Questionnaire in each arm, overall and by cycle, were similar to that for the EORTC QLQ-C30 questionnaire.

Table 29 presents EQ-5D Index and EQ-VAS overall treatment comparisons for the ITT population using longitudinal mixed-effects models with random intercepts and slopes with treatment, time, treatment-by-time interaction, and baseline as covariates.

[redacted] with the EORTC QLQ-C30 Global health status/QoL scale.

Table 29: [redacted]

Overall comparison	**Inotuzumab (N = 164)**	**SoC (N = 162)**	**Inotuzumab – SoC**	
	Estimated mean (95% CI)	**Estimated mean (95% CI)**	**Estimated mean (95% CI)**	**p-value**
EORTC QLQ-C30				
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Global health status/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D Index	[redacted]	[redacted]	[redacted]	[redacted]
EQ-VAS	[redacted]	[redacted]	[redacted]	[redacted]

Key: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQoL visual analogue scale; EQ-5D, EuroQoL 5 Dimension questionnaire;

ITT, intent-to-treat; QoL, quality of life; SE, standard error; SoC standard of care.
Source: INO-VATE 1022 CSR[3]

4.8 Subgroup analysis

The NICE scope does not specify any subgroups that are relevant to this submission.

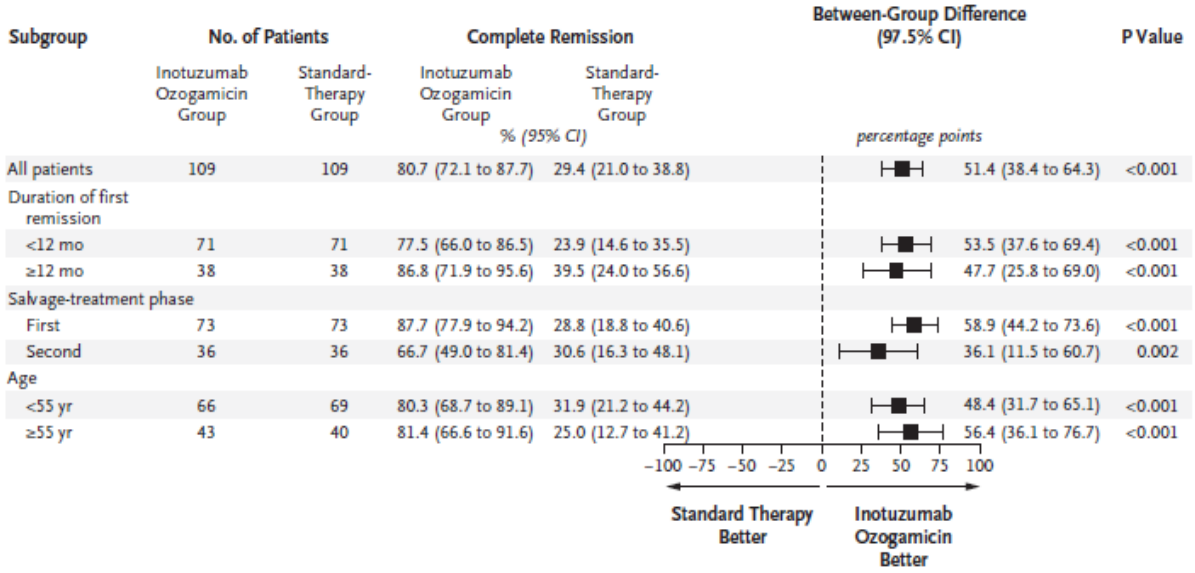
Pre-planned analyses of CR/CRi and OS were performed in subgroups of patients by primary diagnosis and by baseline cytogenetic characteristics in the INO-VATE 1022 trial. Subgroup analyses by age, salvage status, Ph status and prior HSCT status show that inotuzumab efficacy is consistent across different subpopulations. However, results for the Ph+ subgroup did not reach statistical significance, as would be expected with the small sample size, therefore these results are difficult to interpret.

CR/CRi – subgroup analysis

CR/CRi results were in favour of inotuzumab for all subgroups defined by patient stratification factors at randomisation (Figure 14).

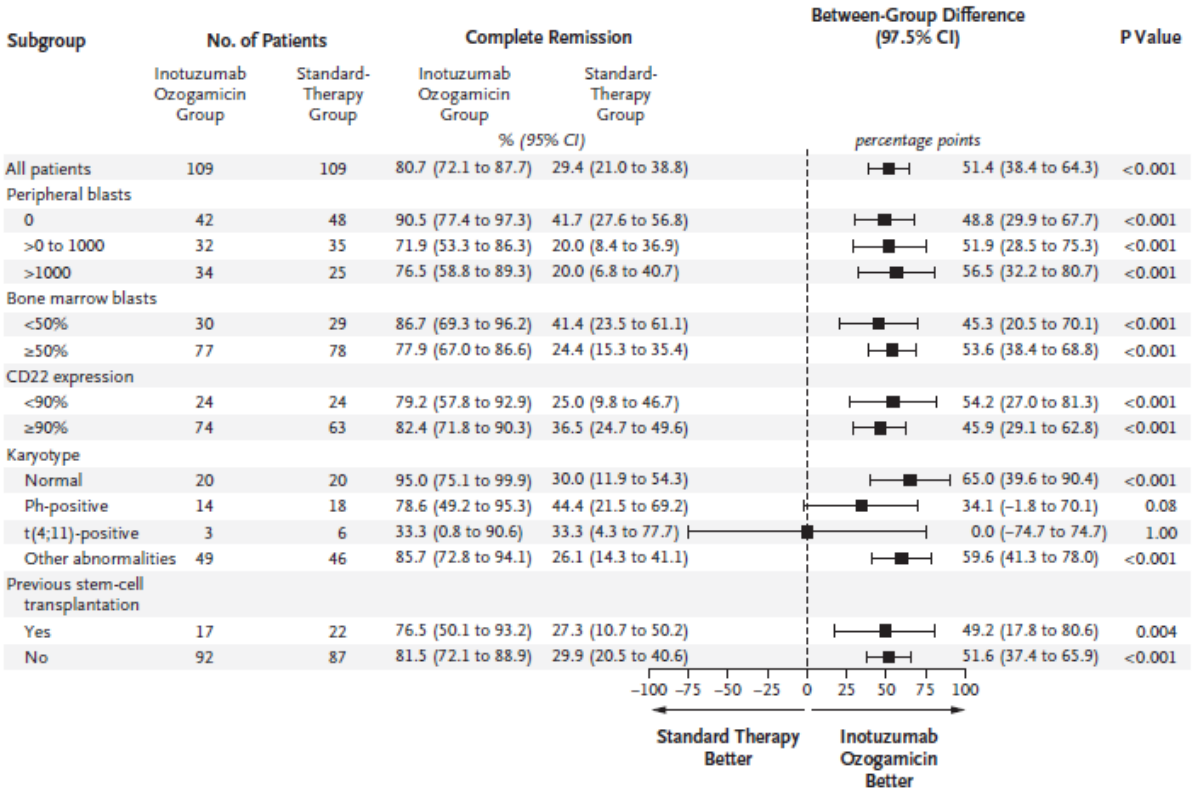
In terms of other patients characteristics at baseline (Figure 15), all CR/CRi results were statistically significantly in favour of inotuzumab, with the exception of the Ph+ and t(4;11)+ cytogenic characteristics. The t(4;11)-positive subgroup had extremely small numbers of patients (3 vs 6 for inotuzumab and the control groups, respectively), so conclusions cannot be drawn. The results for the Ph+ subgroup were still numerically in favour of inotuzumab, with the results approaching statistical significance (p=0.08); however, there are also very small numbers of patients in this group (14 vs 18 for inotuzumab and the control groups, respectively) ultimately limiting the ability of the results to reach statistical significance.

Figure 13: CR/CRi rate according to stratification factors at randomisation



Key: CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete haematologic recovery; mo, months; yr, years.
Source: Kantarjian et al. (2016)[2]

Figure 14: CR/CRi rate according to patient characteristics at baseline



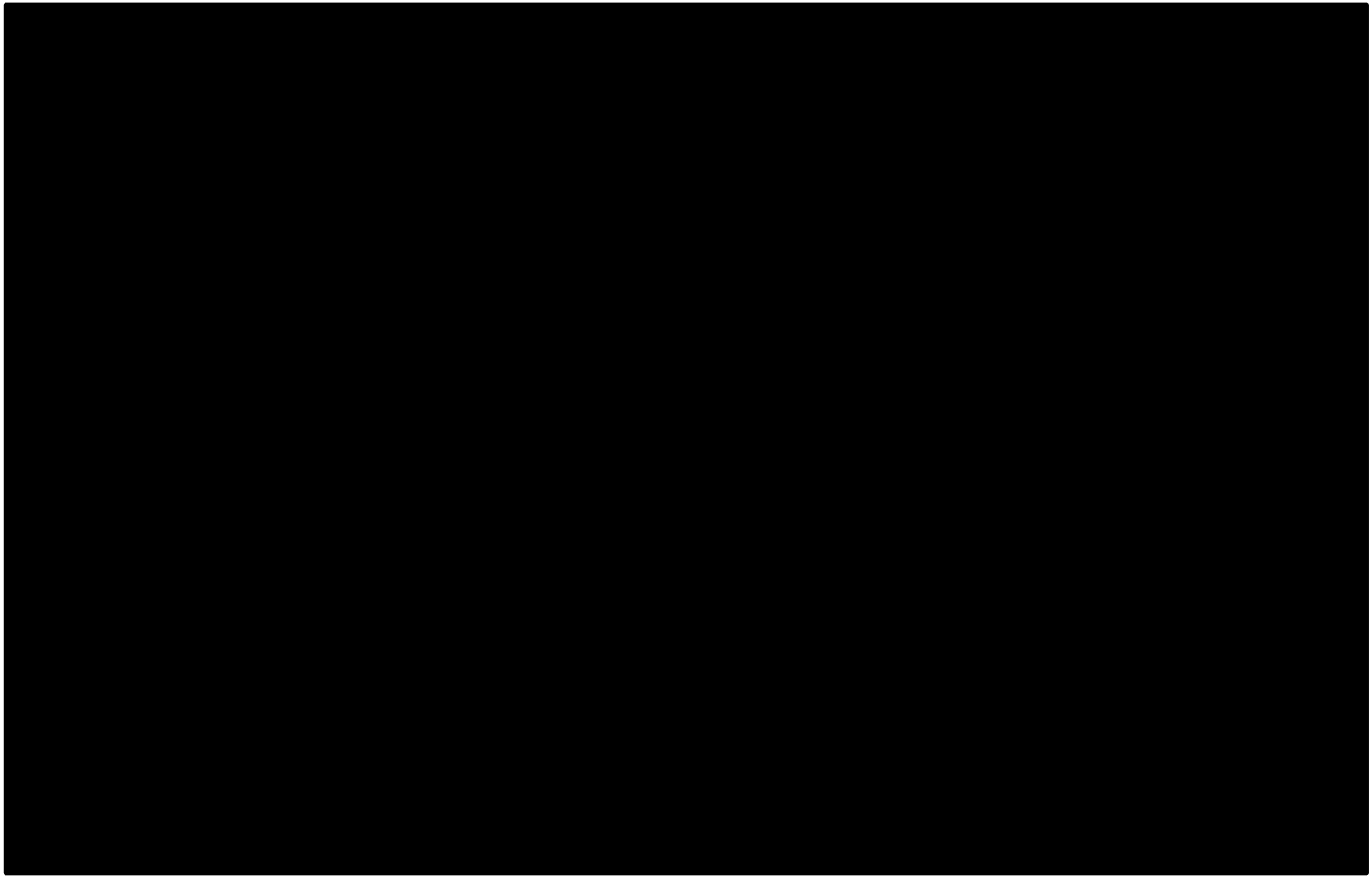
Key: CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete haematologic recovery; Ph, Philadelphia chromosome.
Source: Kantarjian et al. (2016)[2]

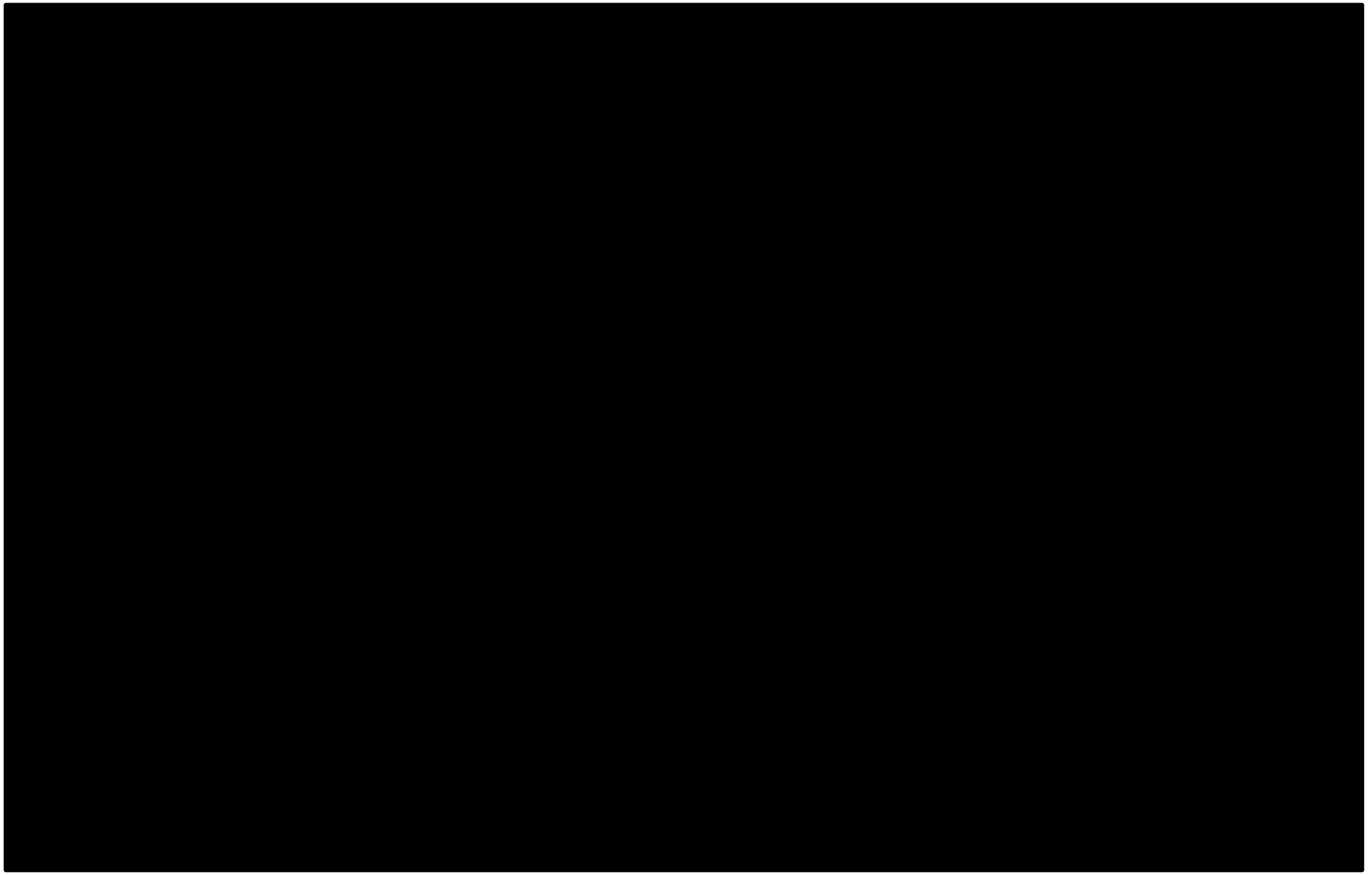
Pre-specified OS – subgroup analysis

In terms of baseline cytogenetic characteristics, the only groups which did not display significant rate differences were for Ph+ patients (rate difference: [redacted]) and t(4:11) patients (rate difference: [redacted]). However, both of these subgroups contained extremely small numbers of patients (6 vs 7 for inotuzumab vs control patients and 22 vs 28 for inotuzumab vs control patients, in the t(4:11) and Ph+ subgroups, respectively) and therefore interpretation of the data is limited.

Forest plots for the subgroup analyses of OS are presented in Figure 16.

15





Key: AE, adverse event; CI, confidence interval; IVRS, interactive voice response system; MRD, minimal residual disease; Ph, Philadelphia chromosome.
Source: INO-VATE 1022 CSR[3]

4.9 Meta-analysis

A meta-analysis has not been performed as evidence came from a single head-to-head RCT.

4.10 Indirect and mixed treatment comparisons

An indirect or mixed treatment comparison was not conducted as not only was head-to-head data available, but no clinical trials investigating treatments relevant to the decision problem with common comparators were identified (in the relevant patient population).

4.11 Non-randomised and non-controlled evidence

Supporting evidence for inotuzumab is also presented from two non-randomised studies:

- An open-label, single-arm, multicentre (within the US), Phase I/II study of inotuzumab in adult patients with R/R CD22-positive ALL (NCT01363297).[116]
- A single-centre (performed at the MD Anderson Cancer Centre), study of inotuzumab (single-dose and weekly schedule) in adult patients with R/R B-cell ALL (the MDACC study).[63]

As relevant head-to-head RCT evidence is available for inotuzumab compared to standard of care, and these non-randomised studies are not used in the comparative efficacy or cost-effectiveness analyses, only limited evidence is presented from these studies within this submission, to support the RCT evidence presented in Section 4.7, which should be considered the primary source of evidence for this submission. Additional data from these supporting studies are available within the CSR for study NCT01363297 or the publications as described below and in Section 4.1.3.

Summary of trial design

Study NCT01363297 was a Phase I/II open-label, single-arm, multicentre (within the US) study adult patients with R/R CD22-positive ALL.

The Phase I study was split into two parts: part 1 was a dose finding study to assess the safety, tolerability, and preliminary efficacy at increasing dose levels of

inotuzumab in this population in order to select the recommended Phase II dose/schedule, and part 2 was a dose-expansion study to further evaluate safety and efficacy at this chosen dose/schedule.

The aim of Phase II of the study was to evaluate the efficacy of inotuzumab, as measured by CR/CRi in patients in second or later salvage setting. Patients received 2 to 3 weekly doses of inotuzumab over a 28-day cycle, and treatment continued until disease progression, patient refusal, unacceptable toxicity, or up to a maximum of 6 cycles, whichever occurred first.

A summary of the study outcomes is presented in Table 30.

Primary Endpoints

During the Phase I dose-finding portion of the study, the percentage of patients with preliminary satisfactory response (defined as achieving CR, CRi, partial response or residual disease) was 100.0% (3/3 patients) for 1.2mg/m^2/cycle, 91.7% (11/12 patients) for 1.6mg/m^2/cycle, and 88.9% (8/9 patients) for 1.8mg/m^2/cycle. The CR/CRi rate was 66.7% (2/3 patients; [95% CI: 9.4, 99.2]) for 1.2mg/m^2/cycle, 75.0% (9/12 patients; [95% CI: 42.8, 94.5]) for 1.6mg/m^2/cycle, and 88.9% (8/9 patients; [95% CI: 51.8, 99.7]) for 1.8mg/m^2/cycle. For the Phase I dose-expansion portion of the study, the CR/CRi rate was 46.2% (6/13 patients; [95% CI: 19.2–74.9]).

For the Phase II portion of the study, the CR/CRi rate was 68.6% (24/35 patients; [95% CI: 50.7, 83.2]; [90% CI: 53.4–81.3]) [CR rate = 28.6% (10/35 patients)]. One-sided p-value for H_0: CR/CRi rate ≤20% was <0.0001. Therefore, the primary objective for the CR/CRi rate in the Phase II portion of the study was met.

For both portions of the study, the CR/CRi rate was 68.1% (49/72 patients; [95% CI: 56.0, 78.6]; CR rate = 31.9% [23/72 patients], CRi rate = 36.1% [26/72 patients]).

Subsequent HSCT

Overall, 24/72 (33.3%) patients underwent HSCT after study therapy. The majority of patients proceeding to HSCT achieved CR/CRi (22/72 [30.6%]) with inotuzumab prior to HSCT.

Table 30: Summary of preliminary satisfactory response, haematologic remission, haematologic response and SCT rate

	Phase I				Phase II	
	Dose-finding			Dose-expansion		
	1.2mg/m^2 (N = 3)	1.6mg/m^2 (N = 12)	1.8mg/m^2 (N = 9)	1.8mg/m^2 (N = 35)	1.8mg/m^2 (N = 35)	All doses (N = 72)
Preliminary satisfactory response[a], n (%)	3 (100.0)	11 (91.7)	8 (88.9)	NA	NA	NA
CR/CRi, n (%)	2 (66.7)	9 (75.0)	8 (88.9)	6 (46.2)	24 (68.6)	49 (68.1)
• 95% CI[b]	9.4, 99.2	42.8, 94.5	51.8, 99.7	19.2, 74.9	50.7, 83.2	56.0, 78.6
• 90% CI[b]					53.4, 81.3	
• p-value[c]					<0.0001	
CR/CRi/PR, n (%)	2 (66.7)	11 (91.7)	8 (88.9)	6 (46.2)	26 (74.3)	53 (73.6)
• 95% CI[b]	9.4, 99.2	61.5, 99.8	51.8, 99.7	19.2, 74.9	56.7, 87.5	61.9, 83.3
• CR	1 (33.3)	7 (58.3)	3 (33.3)	2 (15.4)	10 (28.6)	23 (31.9)
• CRi	1 (33.3)	2 (16.7)	5 (55.6)	4 (30.8)	14 (40.0)	26 (36.1)
• PR	0	2 (16.7)	0	0	2 (5.7)	4 (5.6)
Patients with post-treatment HSCT, n (%)	0	9 (75.0)	4 (44.4)	3 (23.1)	8 (22.9)	24 (33.3)
Time to HSCT, days[d]						
• n	0	9	4	3	8	24
• Mean (SD)	NA	40.8 (12.64)	62.0 (21.65)	74.0 (17.69)	57.5 (39.62)	54.0 (27.53)
• Median (range)	NA	36.0 (20–60)	61.5 (41–84)	77.0 (55–90)	40.0 (27–148)	45.5 (20–148)

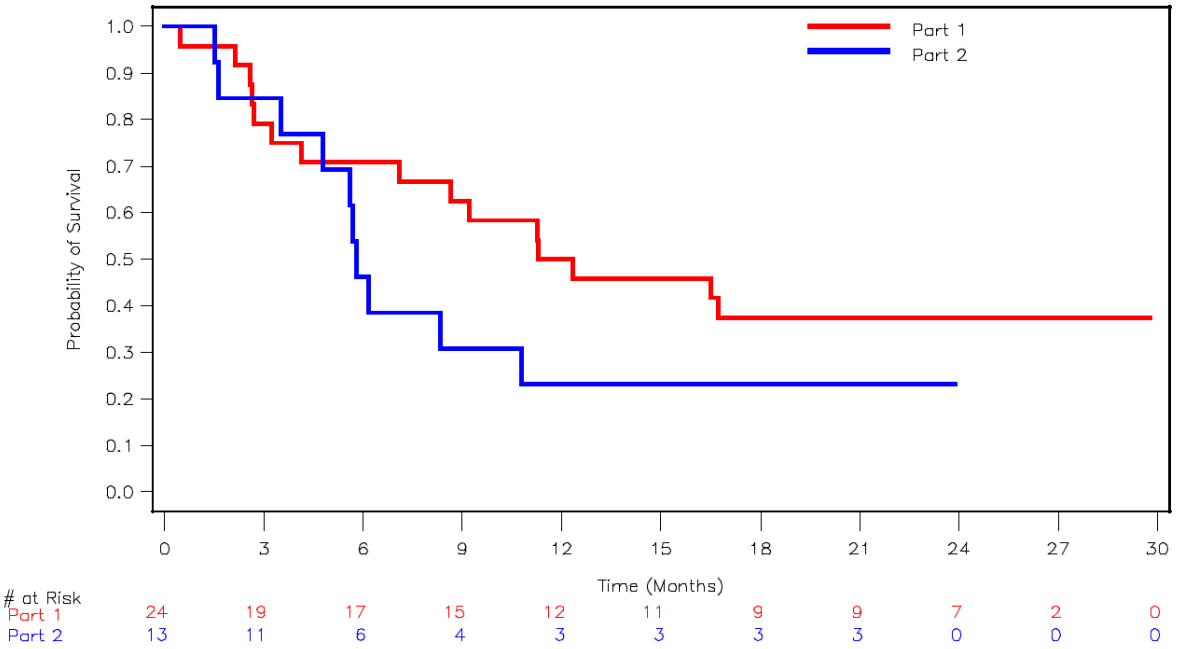
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; H_0, null hypothesis; HSCT, haematopoietic stem cell transplant; NA, not applicable; PR, partial response; RD, residual disease; SD, standard deviation.
Notes: [a], Patients who achieved CR, CRi, PR, or RD after receiving the first dose of treatment. [b], CI created by Exact Binomial approximation. [c], One-sided p-value for H_0: CR+CRi ≤20% using binomial distribution. [d], Time to HSCT was defined as the time from the date of last dose of inotuzumab to the date of HSCT.
Source: NCT01363297 CSR[116]

Other secondary endpoints

Overall, of the 49 patients who achieved CR/CRi, 41 (83.7%) patients also achieved MRD-negativity. The median time to MRD-negativity was 29.0 days (range: 21–141 days). In the Phase II portion of the study, of the 24 patients who achieved CR/CRi, 18 (75.0%) patients also achieved MRD-negativity. The median time to MRD-negativity was 25.5 days (range: 21–80 days). From the overall study, of the 24 patients who progressed to HSCT, the median time to HSCT was 45.5 (range: 20–148 days) (40.0 [range: 27–148] days for the 8 patients who progressed to HSCT in the Phase II portion of the study).

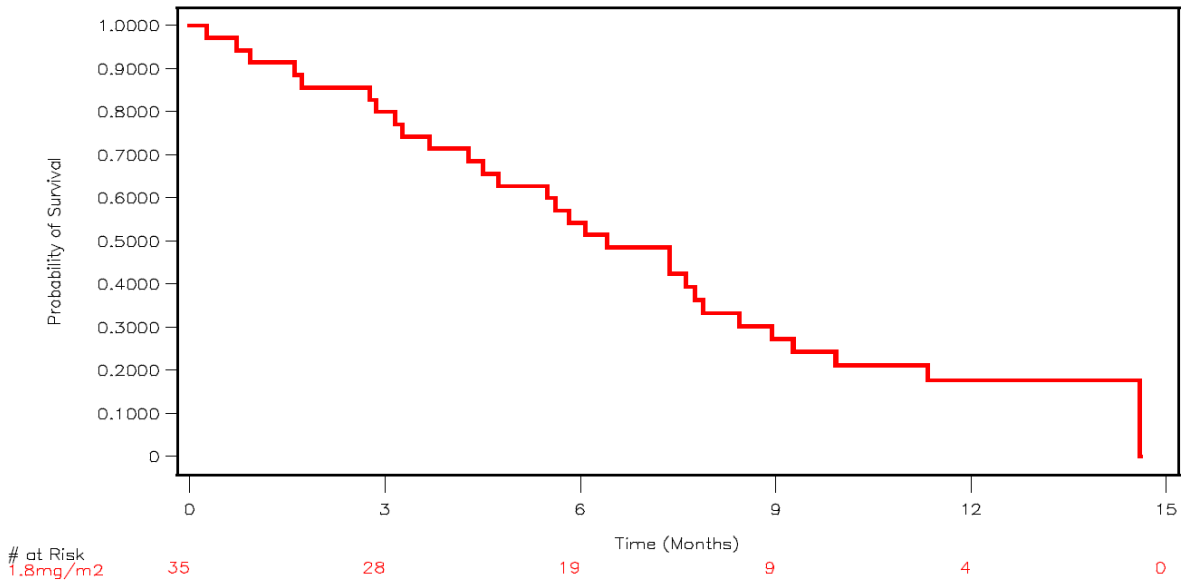
Kaplan–Meier curves for OS are presented in Figure 17 for the Phase I study and Figure 18 for the Phase II study. Overall, 75.0% (54/72) of patients died (i.e. 18 [25.0%] patients were censored). Overall, the median OS was 7.4 months (95% CI: 5.7, 9.2) without censoring for HSCT and little difference was seen when censored for HSCT, as a result of small patient numbers. In the Phase II portion of the study, 29/35 (82.9%) patients died (i.e. 6/35 [17.1%] patients were censored). In the Phase II portion of the study, the median OS was 6.4 months (95% CI: 4.5, 7.9) without censoring for HSCT. The same median and CI were observed with five additional patients censored for HSCT.

Figure 16: Kaplan–Meier plot of OS – Phase I



Key: #, number; OS, overall survival.
Notes: Part 1 was the Phase I dose-finding portion and Part 2 was the Phase I dose-expansion portion.
Source: NCT01363297 CSR[116]

Figure 17: Kaplan–Meier plot of OS – Phase II

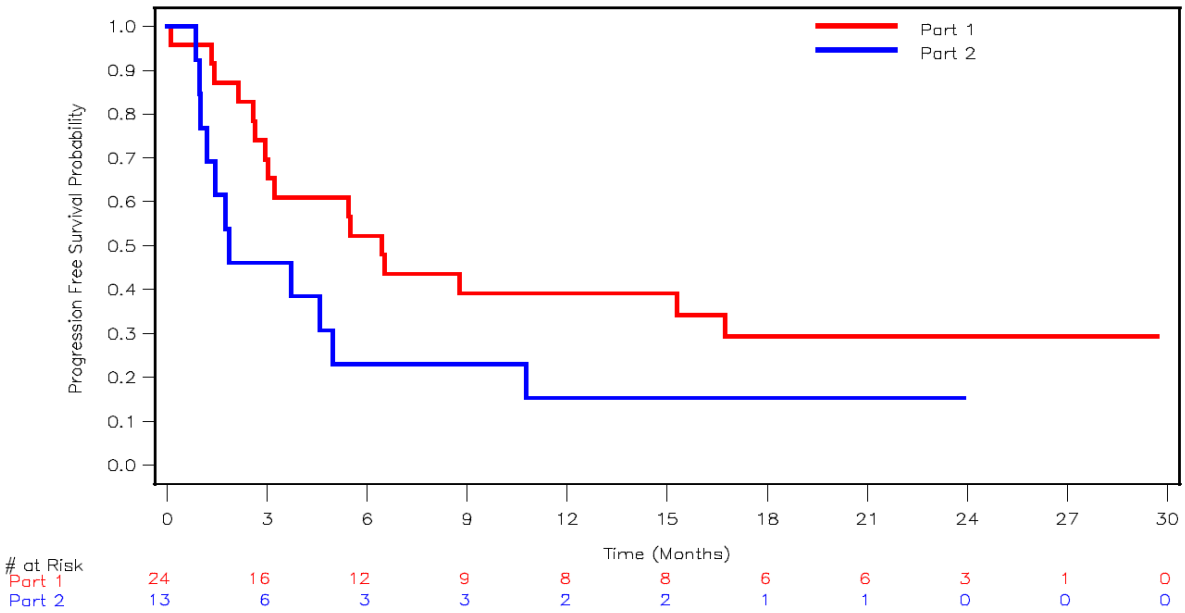


Key: #, number; OS, overall survival.
Source: NCT01363297 CSR[116]

Of the 49 patients who achieved CR/CRi, 35 patients (71.4%) had a subsequent event (i.e. PD, death, other). The median duration of remission was [redacted] months (95% CI: 3.8–6.6) without censoring for HSCT. The median duration of remission was 4.3 months (95% CI: 3.8–5.6) with 9 additional patients censored for HSCT. In the Phase II portion of the study, of the 24 patients who achieved CR/CRi, 20 patients (83.3%) had a subsequent event. The median DoR was 3.8 months (95% CI: 2.2, 5.8) without censoring for HSCT. Similar results were observed with 4 additional patients censored for HSCT (median DoR = 3.8 months [95% CI: 2.2, 4.2]). However, as with the evidence from the INO-VATE 1022 trial, DoR is confounded by the subsequent HSCT, and therefore, PFS is likely to be a more robust measure of inotuzumab efficacy.

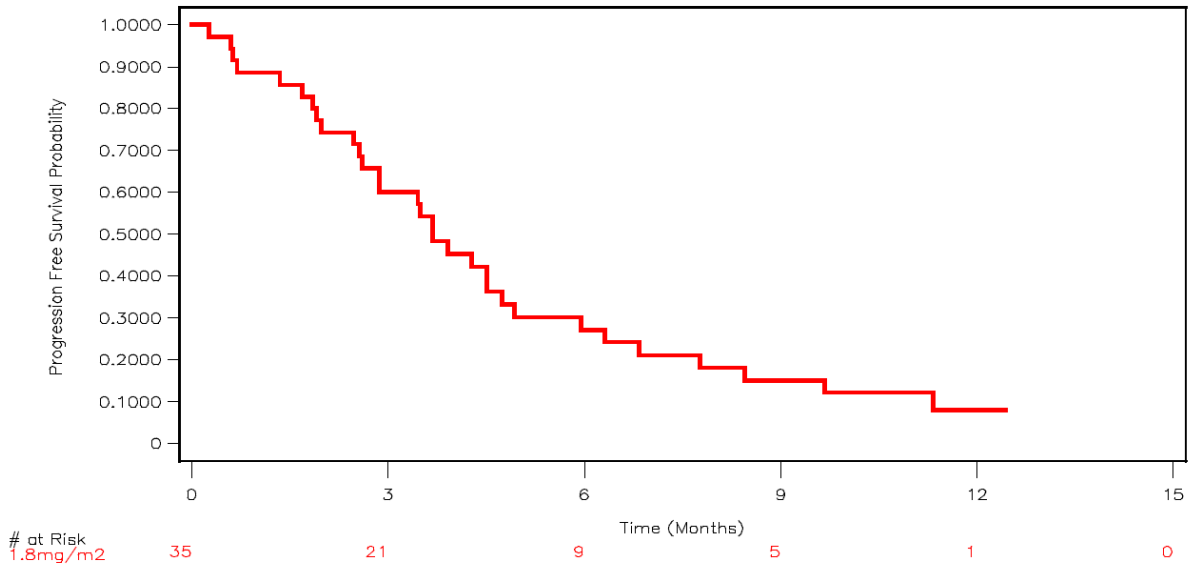
Kaplan–Meier curves for PFS are presented in Figure 19 for the Phase I study and Figure 20 for the Phase II study. Overall, 58/72 (80.6%) patients had PFS events (i.e. 14 [19.4%] patients were censored). The median PFS was 3.9 months (95% CI: 2.9, 5.4) without censoring for HSCT and 4.5 months (95% CI: 3.0, 5.4) with 10 additional patients censored for HSCT. In the Phase II portion of the study, 31/35 (88.6%) patients had PFS events (i.e. 4/35 [11.4%] patients were censored). The median PFS was 3.7 months (95% CI: 2.6, 4.7) without censoring for HSCT. The same median and CI were observed with 4 additional patients censored for HSCT. However, PFS results for the dose-finding and the dose-expansion portions are considered difficult to interpret due to small sample sizes.

Figure 18: Kaplan–Meier plot of PFS – Phase I



Key: #, number; PFS, progression-free survival.
Notes: Part 1 was the Phase I dose-finding portion and Part 2 was the Phase I dose-expansion portion.
Source: NCT01363297 CSR[116]

Figure 19: Kaplan–Meier plot of PFS – Phase II



Key: #, number; PFS, progression-free survival.
Source: NCT01363297 CSR[116]

The MDACC study

Summary of trial design for the MDACC study

The MDACC study was an observational study of patients with R/R B-cell ALL. Only data for patients treated with inotuzumab, in line with the decision problem, are presented here.

The first 49 patients in the study were treated with single-dose inotuzumab 1.3-1.8mg/m^2 by I.V. every 3-4 weeks. In the next 41 patients the dosing was modified to a fractionated weekly schedule: 0.8mg/m^2 on day 1 and 0.5mg/m^2 on days 8 and 15, every 3-4 weeks.

The MDACC study included some patients aged ≤18 years (7% of the overall study population), so is not directly comparable to the scope of this submission. However, as the number of paediatric patients were so small, the evidence can still be considered to support the main evidence presented from the INO-VATE 1022 trial, but relevant interpretation is limited.

Outcomes in the MDACC study

Table 31 presents a summary of the main outcomes of the MDACC study.

Table 31: Outcomes in the MDACC study

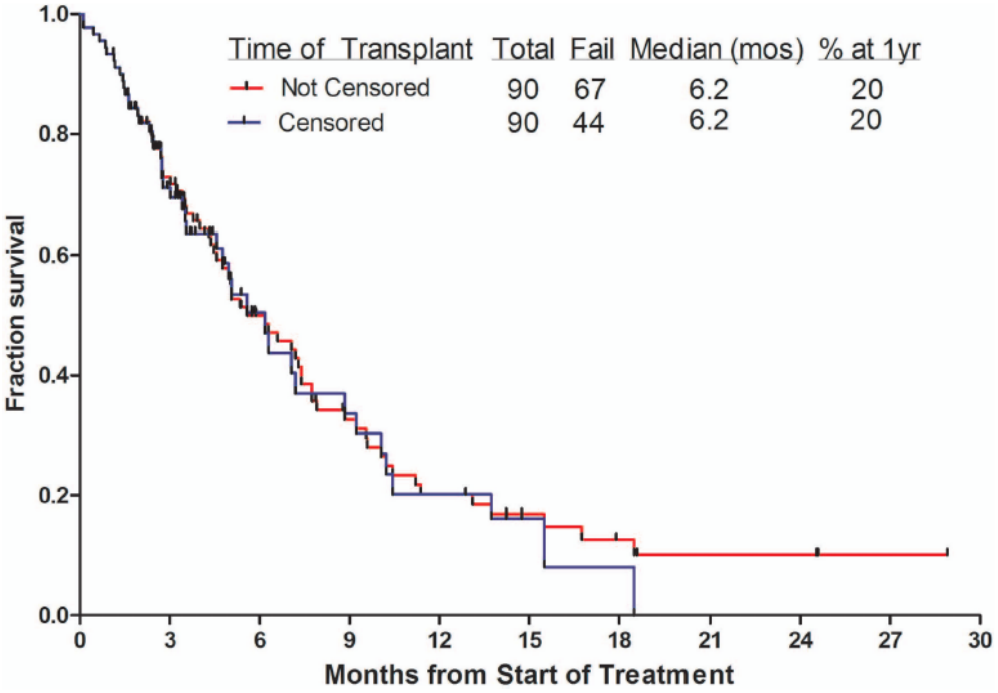
Outcome	**Inotuzumab**		
	Single-dose (n=49)	**Weekly dose (n=41)**	**Overall (n=90)**
Number of cycles of treatment, median (range)	2 (1-5)	2 (1-6)	NR
Response, n (%)			
CR	9 (18)	8 (20)	17 (19)
CRp	14 (29)	13 (32)	27 (30)
CRi (marrow CR)	5 (10)	3 (7)	8 (9)
PR	0 (0)	0 (0)	0 (0)
Resistant	19 (39)	15 (37)	34 (38)
Death <4 weeks	2 (4)	2 (5)	4 (4)
MRD negativity, overall population, n (%)	**N = 49**	**N = 40**	**N = 89**
	19 (39)	17 (42)	36 (40)
MRD negativity,	NR	NR	**N = 50**

patients with CR, n (%)			
	NR	NR	36 (72)
OS, median, months	5.0	7.3	6.2
Response duration			
Median, months	NR	NR	7
1-year rate	NR	NR	42%

Key: CR, complete remission (defined as disappearance of all disease with marrow blasts 5% or less, neutrophils ≥1.0×10^9/L, and platelet count>100×10^9/L; CRi, complete remission without recovery of platelets to ≥100×10^9/L or neutrophil counts to ≥10^9/L; CRp, complete remission without platelet recovery to ≥100×10^9/L.
Source: Kantarjian, 2013[63]

Figure 21 presents the Kaplan–Meier curve for OS, with and without censoring for HSCT for the overall study group in the MDACC study.

Figure 20: Survival in the MDACC study with and without censoring for HSCT



Key: mos, months.
Source: Kantarjian, 2013[63]

An analysis of the MDACC data was performed only for adult patients in the Jabbour et al., (2016) paper.[17] This analysis included 75 patients treated with inotuzumab and 54.7% achieved CR, CRp (defined as CR without platelet recovery to ≥100×10^9/L) or

CRi (defined as CR without recovery of platelets to ≥100×109/L or neutrophil counts to ≥109/L) (CR = 16%; CRp = 34.7%; CRi = 4%). Of the 41 patients who achieved CR, CRp or CRi, 21 were in salvage one and 20 were in salvage two. Among patients who achieved remission, MRD negativity was noted in 41% (43% who received inotuzumab as salvage one and 40% for salvage two).

4.12 Adverse reactions

Patients treated with inotuzumab were treated for a median duration of 8.9 weeks (range: 0.1, 26.4) compared to 0.9 weeks (range: 0.1, 15.6) for patients in the control group. Inotuzumab patients started a median of 3 cycles of therapy (range: 1, 6) compared to only 1 cycle (range: 1, 4) for patients in the control group. Given the difference in the number of cycles of treatment received and more patients in the SoC arm going on to receive subsequent treatments (and subsequent treatment-emergent adverse events [TEAEs] were not collected), a summary of TEAEs and specific TEAEs occurring in ≥5% of patients are presented for Cycle 1 only, as well as for all cycles, to allow a more appropriate comparison of AEs between the treatment groups, which occurred while receiving the relevant treatment.

Table 32 presents a summary of TEAEs for all cycles and Cycle 1 only in the safety population.

Across all cycles, [redacted]%) patients in the inotuzumab arm and [redacted]%) patients in the control arm reported TEAEs, and during Cycle 1 only, [redacted]%) patients in the inotuzumab arm and [redacted]%) patients in the control arm reported TEAEs.

Across all cycles, [redacted]%) patients in the inotuzumab arm and [redacted]%) patients in the control arm reported severe adverse events (SAEs). However, during Cycle 1 only, [redacted]%) patients in the inotuzumab arm and [redacted]%) patients in the control arm had SAEs.

Across all cycles, 147 (89.6%) patients in the inotuzumab arm and [redacted]%) patients in the control arm reported Grade 3 or 4 TEAEs. However, during Cycle 1 only, [redacted]%) patients in the inotuzumab arm and [redacted]%) patients in the control arm reported Grade 3 or 4 TEAEs.

Table 32: Summary of adverse events in INO-VATE 1022 (safety population)

	All cycles		Cycle 1 only	
	Inotuzumab (N=164)	**SoC (N=143)**	**Inotuzumab (N=164)**	**SoC (N=143)**
Patients evaluable for AEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of AEs	[redacted]	[redacted]	[redacted]	[redacted]
n (%)				
AEs	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
Temporary discontinuations due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
Both temporary discontinuation and dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; SAE, severe adverse event; SoC, standard of care.				

Table 33 presents TEAEs across all cycles by system organ class and preferred term that occurred in ≥5% patients in either treatment arm, for all cycles and Cycle 1 only.

Overall, the most common (≥50% in either arm), both across all cycles and for Cycle 1 only, were:

- Blood and lymphatic system disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Infections and infestations
- Investigations (only across all cycles and not for Cycle 1 only)

The TEAEs that occurred most frequently in the inotuzumab arm generally occurred less frequently than those seen in the control arm (except for neutropenia, fatigue, AST elevation, gamma-glutamyl transpeptidase (GGT) elevation, and hyperbilirubinaemia when considered across all cycles). During Cycle 1 only, there were no TEAEs that occurred more frequently in the inotuzumab group than in the control group. Even across all cycles (with inotuzumab patients receiving a higher number of cycles of treatment on average), there were many more TEAEs that occurred with a higher frequency in the control group than in the inotuzumab group (Table 33).

Table 33: TEAEs reported in ≥5% patients in either treatment arm by MedDRA system organ class and preferred term (all grades) (safety population)

	All cycles		Cycle 1 only	
System organ class preferred term	**Inotuzumab (N=164)**	**SoC (N=143)**	**Inotuzumab (N=164)**	**SoC (N=143)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Any AEs	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
• Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
• Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
• Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
• Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Nausea	[redacted]	[redacted]	[redacted]	[redacted]
• Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
• Constipation	[redacted]	[redacted]	[redacted]	[redacted]
• Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
• Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
• Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
• Abdominal distension	[redacted]	[redacted]	[redacted]	[redacted]
• Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
• Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]

	All cycles		Cycle 1 only	
System organ class preferred term	**Inotuzumab (N=164)**	**SoC (N=143)**	**Inotuzumab (N=164)**	**SoC (N=143)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
• Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
• Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
• Chills	[redacted]	[redacted]	[redacted]	[redacted]
• Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
• Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
• Pain	[redacted]	[redacted]	[redacted]	[redacted]
• Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
• Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
• AST increased	[redacted]	[redacted]	[redacted]	[redacted]
• GGT increased	[redacted]	[redacted]	[redacted]	[redacted]
• ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
• Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
• Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
• WBC count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
• Bacteraemia	[redacted]	[redacted]	[redacted]	[redacted]
• Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
• Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
• Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
• Pneumonia fungal	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Headache	[redacted]	[redacted]	[redacted]	[redacted]
• Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
• Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
• Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]

	All cycles		Cycle 1 only	
System organ class preferred term	**Inotuzumab (N=164)**	**SoC (N=143)**	**Inotuzumab (N=164)**	**SoC (N=143)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
• Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
• Fluid overload	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
• Cough	[redacted]	[redacted]	[redacted]	[redacted]
• Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
• Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
• Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Hyperbilirubinaemia	[redacted]	[redacted]	[redacted]	[redacted]
• VOD	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Back pain	[redacted]	[redacted]	[redacted]	[redacted]
• Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
• Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
• Bone pain	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Rash	[redacted]	[redacted]	[redacted]	[redacted]
• Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
• Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
• Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
• Depression	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
• Fall	[redacted]	[redacted]	[redacted]	[redacted]
• Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Hypotension	[redacted]	[redacted]	[redacted]	[redacted]

	All cycles		Cycle 1 only	
System organ class preferred term	**Inotuzumab (N=164)**	**SoC (N=143)**	**Inotuzumab (N=164)**	**SoC (N=143)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
• Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
• Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; NA, not applicable; SoC, standard of care; TEAE, treatment-emergent adverse event; VOD, veno-occlusive liver disease; WBC, white blood cell.				

TEAEs were classified using a 3-tier approach: Tier-1 TEAEs were pre-specified events of special interest, as listed in the product's safety review plan; Tier-2 TEAEs were those that were considered common (≥5% of any treatment group); and Tier-3 TEAEs were those that were neither Tier-1 nor Tier-2. As Tier-1 TEAEs were considered of special interest they have been presented separately in Table 34.

Table 34: Tier-1 TEAEs by MedDRA system organ class and preferred term

System organ class preferred term	**Inotuzumab (N=164)**	**SoC (N=143)**	**Difference between inotuzumab and SoC**		
	n (%)	**n (%)**	**Rate difference**	**95% CI**	**p-value**
Blood and lymphatic system disorders					
• Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders					
• VOD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations					
• Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications					
• Infusion-related reaction	[redacted]		[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; SoC, standard of care; TEAE, treatment-emergent adverse event; VOD, veno-occlusive disease.					

The Tier-1 TEAE preferred term of thrombocytopenia was more commonly reported in the control arm than in the inotuzumab arm ([redacted]% patients, respectively [p=[redacted]]). Tier-1 TEAE preferred terms for infusion-related reactions were reported for patients in the inotuzumab arm only, but only in a small number of patients ([redacted]% patients [p=[redacted]]). Other Tier-1 TEAEs, with the exception of veno-occlusive disease (VOD) events, were reported at a similar frequency between treatment arms.

VOD events reported for the study were more commonly experienced in the inotuzumab arm than in the control arm ([redacted]% patients, respectively [p<[redacted]]). All cases of VOD were considered TEAEs and SAEs. [redacted] of the [redacted] VOD cases in the inotuzumab arm and [redacted] VOD case in the control arm occurred after an HSCT, which followed study therapy. VOD is a known complication of HSCT, occurring in 10–15% of patients following allogeneic HSCT conditioned with a myeloablative regimen.[16] The occurrence of VOD within the trial is higher than would be expected in UK clinical practice, due to different treatment approaches and experience among the countries and institutions included in the study. Countries and institutions with more experience managing VOD, such as those in the UK, experienced the lowest incidence rates, which were similar to those for chemotherapy patients. In addition, in multivariate analysis, patients who had received dual alkylator conditioning (which is not commonly used in the UK) for HSCT (OR = [redacted]) and older patients (≥55; OR = [redacted]) were more likely to experience VOD. Experience from previous studies shows that the use of one alkylating agent instead of two significantly reduces HSCT-associated VOD in inotuzumab-treated patients (p = [redacted]).[63]

VOD rates were particularly high in Japanese centres. Post-HSCT, [redacted] of Japanese patients in the inotuzumab arm and [redacted] of Japanese patients in the SoC arm experienced VOD, and a larger proportion of inotuzumab patients were treated in a Japanese setting than the SoC arm.[126] In the non-Japanese population, only [redacted] of patients in the inotuzumab arm experienced VOD compared to [redacted] in the SoC arm. Although the patient numbers for Japanese patients in the post-HSCT health state are very small, these data show how the difference in transplantation in Japan may be increasing the overall incidence rates of VOD.

Clinicians considered that the practices used in these centres, were not comparable to UK clinical practice; the key difference being the availability of different treatments (e.g. ThioTEPA is used in Japan, which is associated with an increase in the incidence of VOD, however this is not used in the UK) as well as different patient populations. Therefore, VOD rates in the UK would be expected to be lower.[48]

[redacted] had received a prior HSCT; however, the rate is much lower when patients without prior HSCT were viewed separately.[17] Second HSCT is not currently funded under NHS England, and therefore, rates of VOD would be expected to be much lower in clinical practice. VOD, and its application in the economic model, is discussed in further detail in Section 5.4.4. Defibrotide was not available to all trial patients during the conduct of the trial and therefore many patients with VOD were not able to benefit from this treatment. Now it is more widely available, the rates of VOD and related deaths would be expected to decrease.

Grade ≥3 TEAEs were reported for [redacted]%) patients in the inotuzumab arm and for [redacted]%) patients in the control arm. Table 35 presents a summary of all Grade ≥3 TEAEs experienced in ≥2% patients in either treatment arm.

The most common (≥20% in either arm) all-causality Grade ≥3 TEAEs were neutropenia, thrombocytopenia, febrile neutropenia, leukopenia, anaemia and lymphopenia. All of these most frequently occurring Grade ≥3 TEAEs occurred in a much larger proportion of patients in the control group, with the exception of neutropenia, which occurred in slightly more patients in the inotuzumab group than in the control group ([redacted]%). However, neutropenia is typically only a problem for patients if it leads to negative consequences, such as febrile neutropenia, which occurs much more frequently for control patients ([redacted]%). Bacteraemia also occurs more commonly for control patients ([redacted]%) (Table 35).

Table 35: TEAE Grade ≥3 reported in ≥2% patients in either treatment arm by MedDRA preferred term (all cycles) (safety population)

System organ class preferred term	Inotuzumab (N=164)	SoC (N=143)
	n (%)	n (%)
Any AEs	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

System organ class preferred term	Inotuzumab (N=164)	SoC (N=143)
	n (%)	n (%)
Thrombocytopenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
GGT increased	[redacted]	[redacted]
VOD	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
WBC count decreased	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Neutropenic sepsis	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Haemoglobin decreased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Staphylococcal bacteraemia	[redacted]	[redacted]
GGT increased	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Pneumonia fungal	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]

System organ class preferred term	Inotuzumab (N=164)	SoC (N=143)
	n (%)	n (%)
Klebsiella bacteraemia	[redacted]	[redacted]
Escherichia bacteraemia	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Pseudomonal bacteraemia	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Clostridium difficile colitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Escherichia sepsis	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Blood albumin decreased	[redacted]	[redacted]
Bone marrow failure	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]

Key: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GGT, Gamma-glutamyl transpeptidase; SoC, standard of care; TEAE, treatment-emergent adverse event; VOD, veno-occlusive liver disease; WBC, white blood cell.

4.13 Interpretation of clinical effectiveness and safety evidence

Inotuzumab represents a step-change in disease management in an orphan population for whom there is a poor prognosis and limited treatment options. Inotuzumab utilises a novel, targeted mode of action to limit systemic toxicity in the destruction of cancer cells, which means that it is well-tolerated and has a manageable safety profile compared to other chemotherapy agents. Alongside offering a convenient administration schedule with no requirement for hospitalisation, inotuzumab has demonstrated unprecedented rates of complete remission, significant improvements in MRD negativity, some improvements in HRQL outcomes, and a meaningful survival benefit versus chemotherapy, as well as

improvements in subsequent HSCT rates, which is an important and potentially curative subsequent treatment option for patients with R/R B-cell ALL.

Principal conclusions from the INO-VATE 1022 clinical trial are summarised below:

- Inotuzumab demonstrated significant improvements in CR/CRi versus chemotherapy (80.7% vs 29.4%; p<0.0001)
- Inotuzumab resulted in favourable OS versus chemotherapy (HR = 0.77; p = 0.0203), as well as significantly extending RMST versus chemotherapy (13.9 vs 9.9 months; p=0.0023), which is considered to be a more appropriate analysis of survival in this study
- Treatment with inotuzumab resulted in an approximate four-fold increase in the number of patients proceeding to HSCT versus chemotherapy ([redacted])
  - Inotuzumab patients who achieved CR/CRi and received HSCT had a much higher 2-year survival probability than did patients who did not receive HSCT ([redacted]%)
  - The main direct benefit for patients receiving inotuzumab is the significantly larger proportion of patients achieving CR/CRi, the typical prerequisite for bridging to potentially curative therapies (in this case HSCT)
- Inotuzumab demonstrated significantly better MRD negativity versus chemotherapy (78.4% vs 28.1%; p<0.0001)
  - Patients achieving MRD negativity had greater OS benefit when compared to those who did not achieve MRD negativity ([redacted] months)
- Inotuzumab more than doubled landmark 2-year survival compared to chemotherapy (23% vs 10%)
- Inotuzumab demonstrated improved PFS (5.0 vs 1.8 months; p<0.0001) and a [redacted] DoR ([redacted])
- Inotuzumab demonstrated improvements in PROs when compared to chemotherapy, which included clinically and significantly better physical, [redacted] and role (work/leisure) functioning and [redacted], as measured by EORTC QLQ-C30

- Inotuzumab demonstrated a favourable toxicity profile when compared to chemotherapy
- Inotuzumab is beneficial for all patients with R/R B-cell ALL, regardless of eligibility for HSCT, and while achieving HSCT offers the best chance of long-term survival, the survival benefits of inotuzumab over chemotherapy are independent of receiving HSCT:
  - 80.7% of patients treated with inotuzumab were able to achieve CR/CRi demonstrating that the benefits of inotuzumab are not limited only to the [redacted]% of patients who received HSCT
  - With or without censoring for HSCT, the probability of survival at 24 months is higher in patients treated with inotuzumab than chemotherapy (22.9% versus 9.6%, without censoring for HSCT; [redacted]%, with censoring for HSCT, respectively)
  - Median OS for patients who did not receive follow-up HSCT was 6.7 months in the inotuzumab arm versus 5.5 months in the control arm.

The OS data in the study deviate from the proportional hazards assumption around 15 months (See Section 4.7) and both the HR and median OS estimates are limited in their usefulness for interpretation. Therefore, OS was also analysed using post-hoc restricted mean survival time (RMST) methods (described in more detail in Section 4.7) in order to account for this.

- The rationale for using RMST is presented in Section 4.4. It is an alternative approach to estimate the treatment effect for use especially when the assumption of proportional hazards is not satisfied[4-6], which more appropriately reflects the survival data for when differences are observed in the tail of the curves, as is the case in the INO-VATE 1022 trial.
- RMST methods have been used and accepted in previous NICE submissions in which similar issues were faced, including nivolumab in advanced (unresectable or metastatic) melanoma in adults (TA384)[9] and ipilimumab for adults with previously untreated advanced (unresectable or metastatic) melanoma (TA319).[10]

- The default time point for these analyses in the statistical package corresponds to the shorter of the maximum OS time in the two arms of the study, i.e. looking at the last censored event in each arm and taking the shortest, which was at 24 months. These results have been presented within the submission for consistency. However, the developer of the statistical package recommends that this default timepoint is not used for these analyses, but that a timepoint directly connected to clinical interests or study objectives is used instead.[123] To this end, a timepoint reflecting the maximum observation time from the arms, i.e. 37.7 months, was used to more fully capture the data across the whole trial. (See Section 4.4 for full details of the RMST analysis).

The majority of patients in INO-VATE 1022 were treated with FLAG. Clinicians agreed that FLAG-based chemotherapy is the most commonly used treatment for this patient population in the UK, and therefore the trial can be considered to be reflective of UK clinical practice.[48]

- Patients who are able to receive more intensive therapy, can receive FLAG-IDA. However, a small study of 105 patients with poor risk acute leukaemia or myelodysplastic syndrome who were treated over a 4-year period showed no statistical difference in outcomes between FLAG and FLAG-IDA[96] and clinicians agreed that they could be considered as equivalent.[48]

Patients in the control arm of the INO-VATE 1022 trial demonstrated higher OS than anticipated, likely due to treatment with subsequent post-SoC induction therapy:

- There was a higher frequency of targeted therapy (e.g. [redacted]) use on subsequent induction treatment in the chemotherapy arm versus the inotuzumab arm ([redacted]%, respectively) which may have contributed to the improved OS of the control arm.

The pre-specified DoR results from the trial do not accurately reflect what would be seen in these patients in practice:

- When patients were identified for HSCT they had no further bone marrow samples collected from them, and were therefore effectively censored from the study

  - Therefore, there would have been patients receiving HSCT and still in remission who would not have been included in the analyses, shortening the reported DoR

- Due to the aggressive nature of the disease, patients must proceed to HSCT as soon as a suitable donor is available, assuming they are able.
- Furthermore, the data reporting the pre-specified DoR was an early cut-off as part of the ITT218 population analysis and was difficult to interpret due to censoring of patients.
  - Patients in remission without 'qualifying events' (e.g. relapse from complete remission or death) were censored at the last valid disease and bone marrow assessment, including follow-up disease assessment
- Only patients who achieved CR/CRi were included in the pre-specified DoR analyses.
  - [redacted] the definition of DoR was extended to include all patients in the ITT (and the ITT218) populations, with non-responders being given a duration of remission of zero.
  - [redacted]
- Therefore, PFS (alongside the DoR analyses [redacted]) is considered to be a more appropriate indicator of the efficacy of inotuzumab, specifically the duration of patients' response, and the time that the patient spends in remission.
- Inotuzumab demonstrated significant improvement in PFS (5.0 vs 1.8 months, p<0.0001) and DoR, as [redacted] ([redacted]) over chemotherapy

Generalisability

The generalisability of the INO-VATE 1022 trial data to a UK population is influenced by the rarity of the disease and the heterogeneity of transplant protocols and practice with regards to disease status at transplant.

In line with the product label and the scope for this submission, the pivotal Phase III trial (INO-VATE 1022) and the supporting Phase I/II trial (B1931010) assessed inotuzumab in the treatment of adults with R/R B-cell ALL.

This was a global trial of 326 patients in 19 countries across 4 regions (North America, Europe, Asia and Oceania). Within the trial there were 8 centres in the UK who recruited a total of 9 patients, which represented 2.8% of the overall patient population (4 (2.4%) in the inotuzumab group and 5 (3.1%) in the control group). This is a reasonable proportion of patients for a multicentre study that recruited patients from 19 countries across North America, the EU, Asia and Australia. The EU was itself well represented, comprising 40.9% of the overall study population.

Within the INO-VATE 1022 trial population, various subpopulations, based on age, salvage status, Ph status and DoR from prior treatment, were included for analysis:

- Subgroup analyses by age and salvage status show that inotuzumab efficacy is consistent across these different subpopulations
- Results for Ph+ were not statistically significant. However, there were very small patient numbers within this subgroup, which is reflective of the overall rates of Ph+ patients in the general population of ALL patients, and the results are therefore extremely difficult to interpret.
- Results for patients who had HSCT prior to the study were worse than for patients who had not received a prior HSCT. These patients are also at higher risk of VOD, which would lead to an increased risk of death in these patients. However, there are low patient numbers within these analyses, and therefore, the results are difficult to interpret. Furthermore, this population is not reflective of the patients that would be seen in clinical practice in England and Wales, where patients would not typically be eligible for a second HSCT in current practice, owing to funding availability.
- However, there is also the potential to use inotuzumab as a bridge to other potentially curative therapies, such as donor leukocyte infusion (DLI), which could be used in patients who have already received HSCT.[48] Therefore, if we also consider the potential for getting patients to receive these other treatment options, then the INO-VATE 1022 trial can be considered to be reflective of UK clinical practice.

- As has been discussed here, although the main benefits of inotuzumab are in enabling more patients to proceed to HSCT, patients are still able to benefit from treatment regardless of HSCT status; with longer OS and higher probability of survival (although there were small patient numbers in this group, and the results did not reach statistical significance).

The number of patients due to receive treatment as a second salvage therapy was limited to 33% of the entire patient population

- This is representative of the typical population that would be seen in clinical practice, where there are typically more patients receiving earlier lines of therapy[127]

To align with the proportion of Ph+ patients that would be expected to be seen in clinical practice, the number of Ph+ ALL patients was limited to approximately 20% of the overall randomised patients

- However, as the prevalence of Ph+ ALL is typically lower than the prevalence of Ph- ALL[57, 58], enrolment of Ph+ ALL patients did not reach 20%, and therefore, no Ph+ ALL patients were excluded due to this limitation, thus representing the real world epidemiology of the disease
- Ph+ prevalence is associated with age, with higher rates of Ph+ in older patients. The proportion of Ph+ patients within the INO-VATE 1022 trial is therefore affected by the age of the patients within the trial. As the trial required patients to be suitable for intensive therapy (in the SoC arm and also subsequent HSCT if possible) this is likely to lead to a relatively younger, fitter trial population, which will impact on the proportion of Ph+ patients.

Overall, the study arms were well balanced in terms of baseline characteristics and were representative of the typical patient population and the outcomes used in the trial were reflective of those that would be used in clinical practice to assess clinical benefit and treatment outcomes.

In INO-VATE 1022, inotuzumab-associated VOD occurred in [redacted]% of patients compared to [redacted]% for placebo patients[75]

- VOD is a known complication of HSCT, occurring in 10–15% of patients following allogeneic HSCT conditioned with a myeloablative regimen[16]

- Countries and institutions with more experience managing VOD had the lowest incidence, similar to the rates for chemotherapy[63]
- In the multivariate analysis, patients who had received dual alkylator conditioning for HSCT (OR = [redacted]) and older patients (≥55; OR = [redacted]) were more likely to experience VOD[75]
- In particular, the [redacted][3]
    - Post-HSCT, [redacted] of Japanese patients in the inotuzumab arm and [redacted] of Japanese patients in the SoC arm experienced VOD, and a larger proportion of inotuzumab patients were treated in a Japanese setting than the SoC arm.[126] In the non-Japanese population, only [redacted] of patients in the inotuzumab arm experienced VOD compared to [redacted] in the SoC arm. Although the patient numbers for Japanese patients in the post-HSCT health state are very small, these data show how the difference in transplantation in Japan may be increasing the overall incidence rates of VOD.
- Experience from the previous studies show that the use of one alkylating agent, instead of two, significantly reduces HSCT-associated VOD in InO-treated patients ($p = 0.02$)[63]
- Effective treatments for and prevention of VOD are available, as recommended by the EBMT[128] and the BSBMT[129]
- As countries with less experience of managing VOD (and therefore higher rates within the INO-VATE 1022 trial) become more experienced in managing these patients, it would be expected that the observed rates of VOD would be much lower, and more in line with those observed for chemotherapy, as was observed within the more experienced centres within the INO-VATE 1022 trial[63]

Limitations of the clinical evidence

Due to the rarity of the condition and a lack of official guidance the patient pathway for R/R B-cell ALL patients is extremely heterogeneous, and is based heavily upon decision making at the individual patient level. Therefore, it is difficult to identify standard of care for these patients, however the majority of patients in INO-VATE 1022 were treated with FLAG, which is specified in the scope.

- Clinicians agreed that FLAG-based chemotherapy was the most commonly used treatment in this patient population and therefore the control arm made up mostly of FLAG-treated patients alongside some other treatments can be considered to be reflective of UK clinical practice.[48]
- TKIs are commonly used alongside chemotherapy-based regimens for Ph+ patients in UK clinical practice. There is evidence to support the use of TKIs in first-line treatment, but there is no comparative evidence to support the use of TKIs in the R/R B-cell ALL population, there are no data available to understand the market share of TKIs in this area, and there is little evidence for TKIs at all in this patient population. However, it is acknowledged as a limitation of the INO-VATE 1022 study design and this submission that TKIs are not used alongside chemotherapy-based treatment for Ph+ patients. There is an attempt to address this within the economic analysis by adding costs for TKI use in Ph+ patients (see Section 5), but there are no data on the incremental efficacy of TKIs in additional to standard therapy in this patient population that could be used.
- There is no comparison to palliative care within a randomised clinical trial – patients within the INO-VATE 1022 trial would not be representative of a patient group that would receive palliative care (as all patients received systemic treatment), and therefore, any comparison to palliative care would be difficult.

Patients who had received prior HSCT were included in INO-VATE 1022, which was not reflective of UK clinical practice.

- Further, a small proportion of patients who received HSCT were non-responders ([redacted] inotuzumab patients vs [redacted] control patients) – this is not reflective of UK clinical practice

- However, there is also the potential to use inotuzumab as a bridge to other potentially curative therapies, such as donor leukocyte infusion (DLI), which could be used in patients who have already received HSCT.[48] Therefore, if we also consider the potential for getting patients to receive these other treatment options, then the INO-VATE 1022 trial can be considered to be reflective of UK clinical practice.
- In the control arm of INO-VATE 1022 patients could receive subsequent induction therapies – this may have overestimated the survival in this arm and affects the proportional hazards assumption; hence why the RMST OS analysis is likely to be a more accurate analysis of comparative survival

Inotuzumab is indicated for patients with R/R B-cell ALL, and has been designated an orphan indication from the EMA. With current therapies, OS (for patients who do not respond to treatment and progress to potentially curative therapies) is as low as 3 months. Treatment with inotuzumab has been shown to significantly extend OS to a mean of 13.9 months with a limited 37.7 month follow-up, compared to a mean of 9.9 months achievable with current standard care. This evidence is summarised in Table 36 and demonstrates that inotuzumab meets end of life criteria.

Table 36: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Adults with relapsed or refractory (R/R) disease experience reported median overall survival as low as 3 months with current therapies[11-13] Median OS in the trial for the control arm (which can be assumed to be representative of UK clinical practice[48]) is 6.7 months using the primary OS analysis and 9.9 months for the RMST OS analysis; both of which are below the 24-month requirement for end-of-life. (See Section 3.4).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Using the RMST analysis, which is considered to be more appropriate in this patient population (Section 4.4), inotuzumab significantly extends OS to 13.9 months vs 9.9 months with chemotherapy (p=0.0023), for a gain in OS of 4-months[75] with a limited 37.7 months of follow-up. Survival outcomes are presented in Section 4.7. The economic model presents mean life years for SoC as 1.49 compared to 6.66 for inotuzumab, again showing an increase of greater than the 3 months required for end of life (see Section 5).
The treatment is licensed	Inotuzumab was assigned orphan designation by the EMA on

or otherwise indicated for small patient populations	7 June 2013.[38] Around 117 patients per year are expected to be eligible for inotuzumab in England and Wales. (See Section 3.4).

4.14 Ongoing studies

No further studies will provide additional evidence for the indication being appraised within the next 12 months. Final OS and safety updates from the INO-VATE1022 trial are expected March 2017.

5. Cost effectiveness

***De novo* cost-effectiveness model**

- The cost-utility of inotuzumab for the treatment of R/R B-cell ALL was assessed with an area-under-the-curve, partitioned survival model. The model included four core health states, each defined by a combination of patients' response to treatment and subsequent receipt (or not) of HSCT: '*No CR/CRi & no HSCT', 'CR/CRI & no HSCT', 'HSCT & Post HSCT' and 'Death'*
- Within each of the core health states (except death), PFS and OS were modelled.
- In the base case analysis, inotuzumab was compared to standard of care, which consists of a combination of FLAG-IDA, HIDAC, CM (in combination with imatinib for Ph+ patients). Each individual treatment within standard of care was also evaluated independently.
- OS and PFS estimates and rate of responses and subsequent transplantation for inotuzumab versus standard of care were based on the INO-VATE 1022 trial data; covariate adjustments for patient characteristics were incorporated into the OS and PFS analysis.
- Health-state utilities were captured within the INO-VATE 1022 trial, and were applied in the model to progression-free patients who did not undergo a HSCT. For the patients undergoing HSCT, health-state utilities were treatment independent and based on the time following HSCT. These values were based on evidence from the literature. For progressed patients, utilities were applied based on the literature.
- Disutilities for adverse events were considered already accounted for in the on-treatment utility; however, a disutility for veno-occlusive disease (VOD) was applied to capture the low quality of life associated with this event.
- Input from expert oncologists who treat ALL patients in the UK was sought to validate the assumptions and the model structure.

Base case results

- In the base case analysis, inotuzumab was associated with a deterministic ICER of £40,013 when discounted at 1.5%, ranging to £55,869 per QALY when 3.5% discounting is applied.
- The NICE Methods Guide suggests a discount rate of 1.5% for benefits in cases where costs or benefits are sustained over a very long period (normally at least 30 years), and inotuzumab is a bridge to HSCT which can restore patients to normal life expectancy.
- The modelled clinical outcomes were validated against clinical outcomes from the evidence base. The model supports a survival advantage associated with inotuzumab as a result of the treatment acting as a better bridge to potentially curative therapy than the standard of care.

Sensitivity analyses

- The probabilistic ICER was similar to the deterministic. However, when uncertainty around post-HSCT survival is introduced, the probabilistic ICER ranges from £48,459 discounted at 1.5%, to £67,575 per QALY when discounted at 3.5%. It should be noted that that uncertainty around post-HSCT survival is most likely to be driven by the efficacy of HSCT, the benefits of which are already established and have been explored within the literature and prior appraisals. Therefore, this uncertainty within the model does not necessarily extend to uncertainty in real UK clinical practice around the use of inotuzumab.
- Scenarios are presented which explore the cost-effectiveness when the model is in line with UK clinical practice, where there is a maximum of 3 treatment cycles or when patients have not had a prior HSCT. In all key scenarios relevant to UK practice, the deterministic ICER is lower than the base case indicating that the base case model is conservative to the true cost-effectiveness of inotuzumab in a UK NHS.

5.1 Published cost-effectiveness studies

5.1.1. Identification of studies

An SLR was undertaken with the objective of identifying cost-effectiveness studies relevant to the decision problem. A secondary objective of this search was to identify cost-minimisation analyses (CMA) and budget impact models (BIM) that would report relevant data to inform the separate cost and resource SLR (Reported in Section 5.5.1). All searches were conducted between 5 and 6 September 2016.

The search strategies used in the electronic searches are provided in full in Appendix 3.1. The databases searched were:

- MEDLINE and Embase (using Embase.com)
- MEDLINE In-Process (using PubMed.com)
- EconLit
- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effectiveness (DARE)
  - National Health Service Economic Evaluations Database (NHS EED)
  - Centre for Reviews and Dissemination – Health Technology Assessment Database (CRD HTA Database)

The searches were limited to those published since 2000 to focus on the most recent cost-effectiveness data. This restriction was applied as considerable changes have been observed in the last 16 years (2000–2016) in relation to costs and resource use, advances in technology (drug therapy, diagnostics, etc.), quality/SoC, the overall standards of living and inflation.

In addition, hand searches of conference proceedings were performed to identify recently completed or ongoing studies of interest. These searches were restricted to the last 2 years and covered the following conferences:

- British Society for Haematology (BSH)
- European Haematology Association (EHA)

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress
- ISPOR Annual International Congress

Additional searches to identify any relevant data were made on the websites listed below:

- EMA (http://www.ema.europa.eu/ema/)
- US Food and Drug Administration (FDA) (http://www.fda.gov/)
- NICE Guidance (http://www.nice.org.uk/)
- CADTH (http://cadth.ca/en/products)
- SMC (http://www.scottishmedicines.org.uk/Home)
- AWMSG (http://www.wales.nhs.uk/sites3/home.cfm?orgid=371)

Bibliographies of key published systematic reviews, economic models and HTAs were also screened to ensure that our initial searches captured all the relevant studies.

The search strategies were designed using search filters validated by the Scottish Intercollegiate Guidelines Network (SIGN). All relevant studies in English were included. Non-English language publications were included and flagged to be explored only if sufficient evidence was not available in the English language publications; however, no non-English articles were identified.

5.1.2. Study selection criteria

The papers identified within the searches were assessed against explicit inclusion/exclusion criteria outlined in Table 37.

In the first instance, primary screening was conducted where each reference (title and abstract) was independently reviewed by one reviewer by applying the basic selection criteria specified in Table 37. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer. The full-text articles were obtained for potentially relevant studies identified by primary screening of titles and abstracts. These studies were independently assessed by one reviewer

against each eligibility criteria. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

Studies that assessed mixed disease populations (e.g. R/R ALL and treatment-naïve ALL or R/R ALL and other malignancy/ies) were included only if separate data were reported for R/R ALL. Similarly, studies that assessed both paediatric and adult patients were included only if subgroup data were available for patients >15 years of age, due to the fact that patients who are 15 years or older can be treated with treatment regimens recommended for adults. Studies were included if at least one treatment arm comprised of an intervention of interest. The relevant cost and resource use data identified from cost-minimisation analyses and budget impact analyses were identified within this review, but were extracted in the cost and resource use review (described in Section 5.5.1). Included studies were categorised based on study country/setting at the secondary screening stage.

Table 37: Inclusion and exclusion criteria for economic modelling studies

Criteria	Inclusion	Exclusion
Population	• Patients aged at least 15 years[a] • Patients diagnosed with R/R ALL	• Paediatric patients • Patients with newly diagnosed ALL
Intervention	Pharmacological interventions for R/R ALL: • Inotuzumab • Blinatumomab • Dasatinib • Imatinib • Ponatinib • Clofarabine • FLAG (fludarabine, cytarabine, granulocyte-colony stimulating factor) • FLAG-IDA combination of fludarabine, cytarabine, idarubicin and G-CSF • HIDAC (high dose cytarabine) • Ara-C plus mitoxantrone • Methotrexate • Asparaginase • Daunorubicin • Cyclophosphamide • Vincristine • Mercaptopurine • Pegaspargase • Doxorubicin	• Any pharmacological treatment not mentioned in the list of included interventions
Comparator	• Placebo • Best supportive care • Any treatment from the list above	• Any pharmacological treatment not mentioned in the list of included interventions • Any non-pharmacological treatment
Outcomes	• ICER • Costs (unit and total)	

Criteria	Inclusion	Exclusion
	• QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities) • Sensitivity analyses results	
Study type	Full economic evaluations, such as: • Cost–consequence • Cost-effectiveness • Cost–utility • Cost–benefit • Cost-minimisation • Budget impact • Systematic review[b]	• Non-systematic reviews, letters and comment articles • Burden of illness studies and non-modelling studies
Language	• Studies published in English • Studies published in non-English languages were included and flagged[c]	• Studies were not excluded based on publication language
Publication timeframe	• Studies published in or after 2000 (last 16 years)	• Published before 2000
Country	• Study inclusion was not restricted to any specific country/region	
Key: ALL, acute lymphoblastic leukaemia; G-CSF, granulocyte-colony stimulating factor; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; RR ALL, relapsed or refractory acute lymphoblastic leukaemia. **Notes:** [a] Patients who were ≥15 years were included for completion as in R/R ALL they may be treated with the treatment regimen recommended for adults; [b] Systematic reviews were included and flagged for bibliography searches; [c] Studies published in languages other than English were to be explored only if sufficient evidence was not identified from English language studies.		

5.1.3. PRISMA flow diagram for the economic SLR

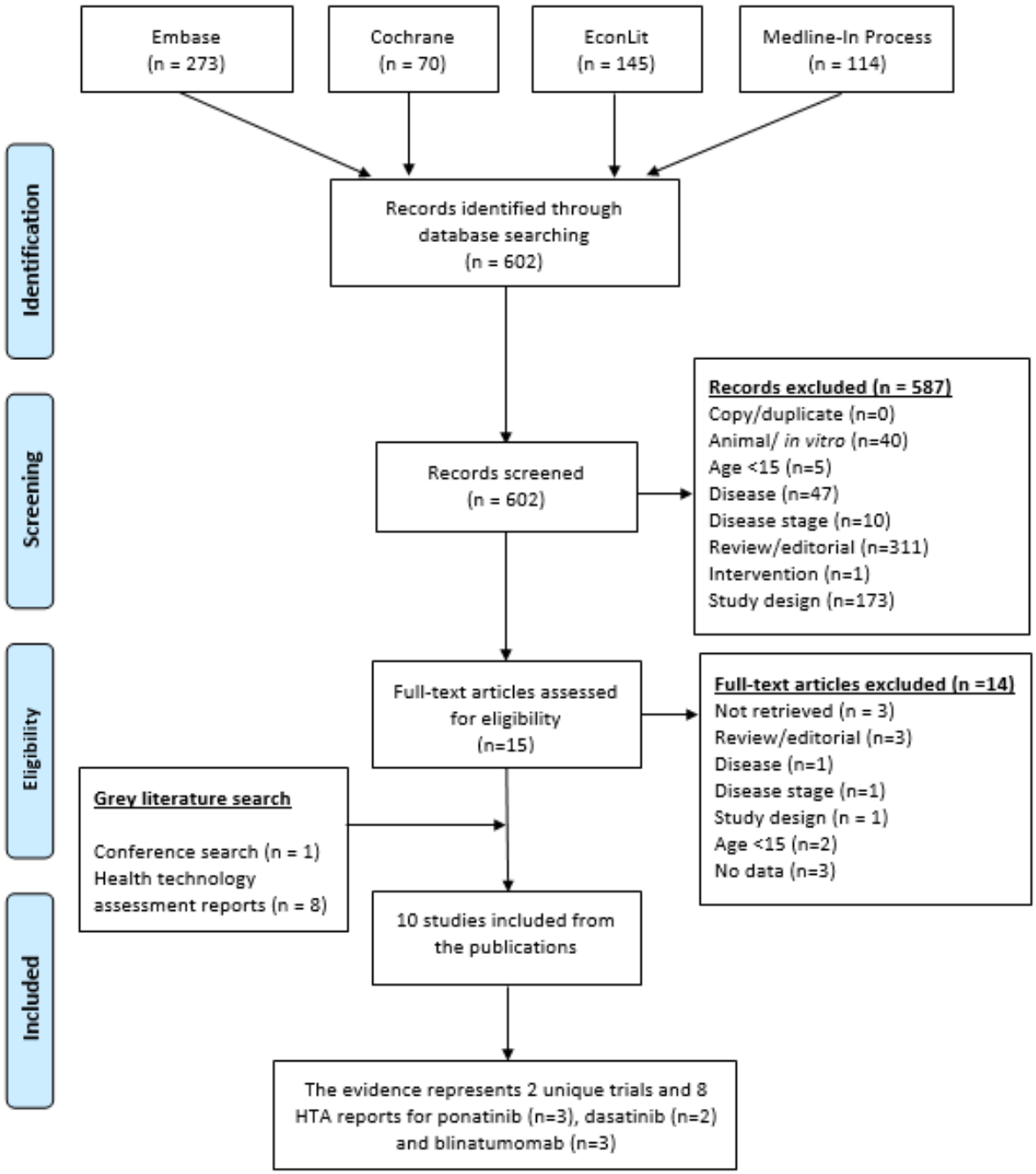
A total of 602 potentially relevant papers or abstracts were identified for the economic evaluations review. These studies were screened based on the information reported in their titles and/or abstracts. Of these, 587 were excluded at the primary screening stage, reasons for exclusion were being review/editorials (n=311), having incorrect study designs (n=173), investigating diseases other than ALL (n=47) and being animal/*in vitro* studies (n=40).

Fifteen articles were assessed in full for further evaluation. Of these, 11 were excluded, and three were unavailable; therefore, one paper was included in the review. Papers were excluded for reasons such as being review/editorials (n=3), having no extractable data (n=3), patients being <15 years old (n=2), having incorrect study designs (n=1), investigating diseases other than ALL (1) and

investigating early stage ALL. Additionally, one abstract and eight HTAs were included from conference searches and websites searches, respectively. Therefore, 10 citations were included for this review.

The details for flow of studies are presented in Figure 22 using a PRISMA flow diagram.

Figure 21: PRISMA diagram for economic modelling studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5.1.4. Overview of included studies

Ten publications were included within the economic review; two were abstracts[130, 131] and eight were HTA appraisals. The HTA appraisals were for the assessment of ponatinib (n=3)[132-134], blinatumomab (n=3)[135-139] and dasatinib (n=2). There were no economic evaluations identified that compared inotuzumab with the required comparators.

Iannazo et al. (2015)[130] reported a health economic (HE) model of patients with Ph+ ALL who were resistant or intolerant to dasatinib. A Markov cohort model assessing the cost effectiveness of ponatinib followed by HSCT in patients who had achieved a major cytogenic response versus best supportive care was described. The analysis was conducted from the UK NHS perspective, with a lifetime horizon, 3-month cycle length and applied discount rates off 3.5% for both costs and outcomes in line with the NICE reference case.[140]

The Mucha et al. 2015 abstract compared to dasatinib and FLAM (fludarabine, cytarabine and mitoxantrone) in the Ph+ ALL population. This study was a Markov model that considered PFS, post-progression survival (PPS) and survival post-HSCT. The model analysis was conducted from the pubic payers' perspective in Poland, and considered a lifetime horizon.

The three ponatinib HTAs were submitted to CADTH, SMC and AWMSG[132-134], and considered only Ph+ ALL patients for whom tyrosine kinase inhibitor (TKI) therapy was inappropriate as a result of resistance or intolerance or presence of T3151 mutation. The cost effectiveness of blinatumomab was assessed by three HTAs (CADTH, SMC and AWMSG) for adult patients with relapsed/refractory Ph- B-cell precursor ALL. Dasatinib was assessed by the SMC and the AWMSG for the indication of adults with Ph+ ALL with resistance or intolerance to prior therapy. A summary of the economic evaluations is presented in Table 38.

Quality assessment was undertaken of the economic evaluations identified within the review. This was conducted using the Drummond and Jefferson economic modelling checklists.[141] Summaries of these assessments are presented in Appendix 3.2.
As no economic evaluations were identified that compared inotuzumab with the relevant comparators, a *de novo* cost-effectiveness model was developed.

Table 38: Key characteristics of economic modelling studies

Study name	Patient population	Intervention/ comparator	Country	Type of study Type of model	Sponsor	Cost year Currency Discount rate	HE perspective Time horizon Cycle length	Model HS Stem cell/BMT was modelled as HS?
Abstracts								
Iannazzo et al., 2015 [a]	Patients with Ph+ ALL who develop resistance or intolerance to dasatinib	Ponatinib[b] BSC	UK	CE Markov cohort model	ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA	2014 Pounds (£) 3.5% for costs and outcomes	UK NHS Lifetime 3-month cycles	Ph+ ALL response, Ph+ ALL no response, post-alloHSCT, adverse event Yes
Mucha 2015	Patients with Ph+ ALL with resistance or intolerance to prior therapy	Dasatinib FLAM	Poland	CU and CE Markov model	NR	NR € 5% for costs and 3.5% for benefits	Public payer's Lifetime NR	Survival without progression, survival after allogeneic HSCT, survival after progression, death Yes
HTA – CADTH								
pCODR – ponatinib (Iclusig®)	Patients with Ph+ ALL for whom other TKI therapy is not appropriate[c]	Two economic analyses Ponatinib vs allogenic HSCT Ponatinib vs palliative BSC (hydroxyurea)	Canada	CU and BIA Markov model	ARIAD Pharmaceuticals, Inc.	NR Dollars ($) NR	NR Lifetime (20 years) NR	NR NR
pCODR – blinatumomab (Blincyto®)	Adult patients with relapsed/ refractory Ph- B-cell precursor	Blinatumomab Salvage therapy with hyper-CVAD[d]	Canada	CU, CE and BIA Partitioned survival model	Amgen Canada Inc.	2015 Dollars ($) NR	Government health payer 50 years NR	Remission (CR; CRh; CRsg), PD and death No

Study name	Patient population	Intervention/ comparator	Country	Type of study Type of model	Sponsor	Cost year Currency Discount rate	HE perspective Time horizon Cycle length	Model HS Stem cell/BMT was modelled as HS?
	ALL							
HTA – AWMSG								
blinatumomab (Blincyto)	Adult patients with relapsed/ refractory Ph- B-cell precursor ALL	Blinatumomab SoC: FLAG-IDA	Wales (UK)	CU and BIA Markov model	Amgen Ltd	NR Pounds (£) 3.5% for costs and outcomes	NHS Wales Lifetime NR	Remission (CR; CRh; CRsg), PD and death No
Dasatinib (Sprycel®) advice no. 1407	Adults with Ph+ ALL with resistance or intolerance to prior therapy	Dasatinib Imatinib SCT	Wales (UK)	CU and BIA Markov model	Bristol-Myers Squibb Pharmaceuticals Ltd	Inflated to 2006 (CU) and 2008 (BIA) Pounds (£) Cost and outcomes discounted at 3.5%	NHS Wales Lifetime (CU) 5 year (BIA) 1 month	Initial best response, no initial response or death No
Ponatinib (Iclusig) Ref number: 1163	Patients with Ph+ ALL[e]	Ponatinib SCT BSC[f]	Wales	CE and BIA Markov cohort model	NR	NR Pounds (£) Cost and outcomes discounted at 3.5%	NHS Wales Lifetime 3 month	Active treatment, allo-SCT, BSC and death[g] Yes
HTA – SMC								
Blinatumomab (Blincyto) SMC No. 1145/16	Adult patients with relapsed/ refractory Ph- B-cell precursor ALL	Blinatumomab SoC: FLAG-IDA	Scotland (UK)	CU Decision analysis model	Amgen Europe B.V.	2016 Pounds (£) 3.5% for outcomes	NHS Scotland Lifetime for patients aged 40 years at the start of the model NR	Remission (CR; CRh; CRsg), PD (PD; aplastic bone marrow or PR) and death Yes

Study name	Patient population	Intervention/ comparator	Country	Type of study Type of model	Sponsor	Cost year Currency Discount rate	HE perspective Time horizon Cycle length	Model HS Stem cell/BMT was modelled as HS?
Dasatinib (Sprycel) SMC No. 371/07	Adults with Ph+ ALL with resistance or intolerance to prior therapy	Dasatinib Imatinib BMT	Scotland (UK)	Economic analysis (but not given clearly) NR	Bristol-Myers Squibb Pharmaceuticals Ltd	NR NR NR	NHS Scotland NR NR	NR NR
Ponatinib (Iclusig) SMC No. 1032/15	Patients with Ph+ ALL^	Two economic analysis: Ponatinib vs SCT Ponatinib vs BSC	Scotland	CU and BIA NR	ARIAD Pharmaceuticals, Inc.	NR Pounds (£) NR	NHS Scotland Lifetime NR	NR NR

Key: ALL, acute lymphocytic leukaemia; AWMSG, All Wales Medicines Strategy Group; BIA, budget impact analysis; BMT, bone marrow transplant; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CE, cost effectiveness; CR, complete remission; CRh, complete remission with partial haematological recovery; CRsg, complete remission by study group; CU, cost utility; FLAM, fludarabine, cytarabine and mitoxantrone; FLAG-IDA, combination of fludarabine, cytarabine, idarubicin and granulocyte-colony stimulating factor (G-CSF); HE, health economic; HS, health states; HSCT, haematopoietic stem cell transplantation; HTA, health technology assessment; hyper-CVAD, hyper fractionated-CVAD: cyclophosphamide, vincristine, doxorubicin and dexamethasone; NHS, National Health Service; NR, not reported; pCODR, pan-Canadian Oncology Drug Review; PD, progressive disease; Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; PR, partial remission; SMC, Scottish Medicines Consortium; SoC, standard of care; TKI, tyrosine kinase inhibitor.

Notes: [a] Poster associated with abstract was also identified; [b] Followed by alloHSCT in patients who achieve major cytogenic response; [c] Not appropriate, i.e. T315I mutation positive or where there is prior TKI resistance or intolerance; [d] Hyper-CVAD (hyper fractionated; CVAD: Course A: cyclophosphamide, vincristine, doxorubicin and dexamethasone + Course B-Methotrexate, cytarabine as per the Sunnybrook Hospital protocol); [e] Patients who are resistant/intolerant to dasatinib; for whom subsequent treatment with imatinib is not clinically appropriate or who have the T315I mutation.

[f] Comparator treatment sequences for the Ph+ ALL indication were based on whether patients were suitable or unsuitable for SCT.
For patients who were suitable for SCT, the relevant treatment sequences were:
• Ponatinib, followed by SCT (Ponatinib, SCT) in those patients who respond to it; BSC is applied after ponatinib discontinuation
• Entire modelled population starts on SCT (SCT)
For those patients not suitable for SCT, the relevant treatment sequences were:
• Ponatinib treatment, followed by BSC in case of discontinuation
• Patients are only given palliative chemotherapy (BSC)

[g] Patients start in the 'Active Treatment' state if the comparator is ponatinib, in the 'allo-SCT' state if the comparator is allo-SCT and in the 'BSC' state if the comparator is BSC.

5.2 De novo analysis

5.2.1. Patient population

The INO-VATE 1022 trial was the primary source of key clinical data used to inform the cost-effectiveness model. This study, as detailed in Section 0, was a Phase III randomised, multicentre, open-label trial assessing the efficacy of inotuzumab versus investigators choice of chemotherapy in R/R CD22 positive ALL patients. The patient population considered within the economic model is adults with R/R B-cell ALL, in line with the final scope issued by NICE shown in Table 1. The baseline characteristics of weight, age and gender split obtained from the INO-VATE 1022 trial were used to inform the economic model.

5.2.2. Model structure

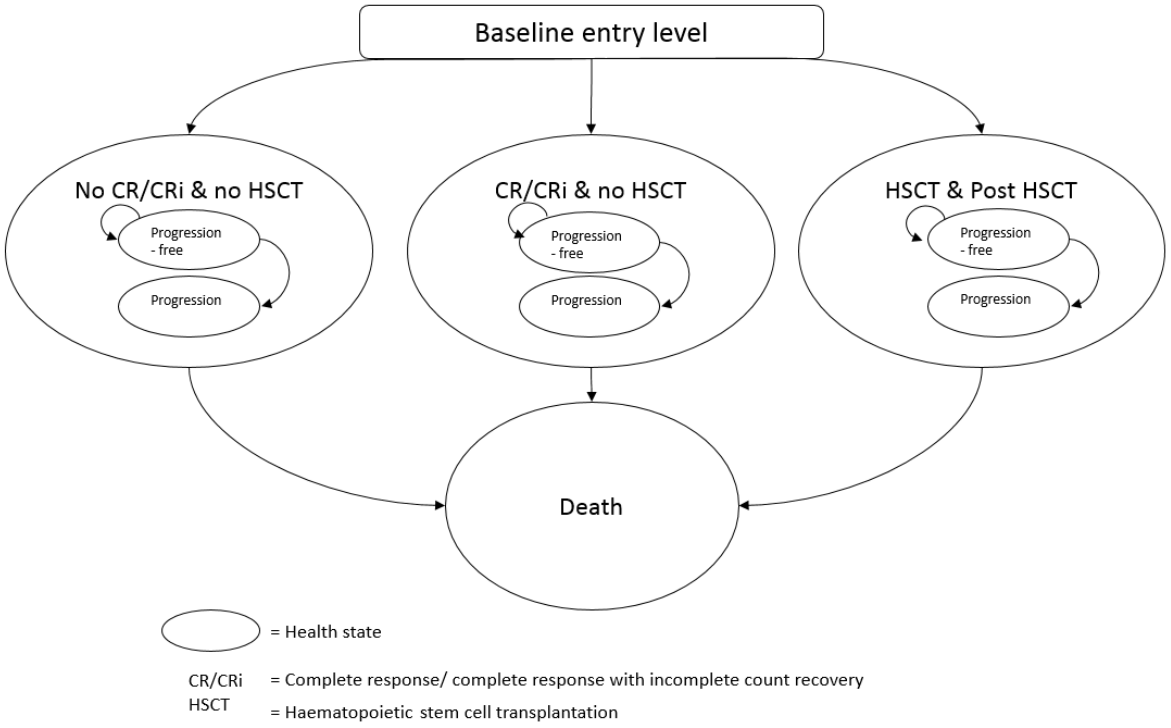
The model was developed using a Markov health state structure to reflect the UK clinical pathway of patients with R/R B-cell ALL. The model structure had four main health states to reflect the disease and the path to potentially curative therapy (HSCT): *'No CR/CRi & no HSCT' 'CR/CRi & no HSCT', 'HSCT & Post-HSCT' (which incorporated patients both CR/CRi and No CR/CRi)* and '*death'*, which was an absorbing state into which patients can transition from any other state. Within each of these main health states (excluding '*death*'), PFS was also modelled. The four main health states were selected in line with the disease where a patients' remission level would be likely to determine their survival in addition, particularly for patients who are ineligible for HSCT (see Section 5.3). In addition, there is evidence to suggest that a patients' quality of life will differ depending upon their response and whether they undergo HSCT[18], therefore it was considered appropriate to model the level of remission and HSCT as different health states.

The main goal of treatment in ALL is to bridge patients to potentially curative therapy, with remission typically a pre-requisite to receive such therapy. Curative therapy gives patients the best chance of improved OS, so achieving CR/CRi is the key outcome. The high CR/CRi rates seen within the INO-VATE 1022 trial illustrate inotuzumab's benefit patients in acting as a bridge to potentially curative therapy, so a key objective of the model was to accurately reflect this treatment benefit.

The model was designed in line with the NICE reference case[140], from the perspective of the UK NHS and PSS. A cycle length of 28 days was used in the model, which was broadly in line with the treatment cycle length of inotuzumab and comparator regimens. In line with standard practice, a half-cycle correction was applied. The starting age in the model is 46 as this was the average age of the ITT population in the INO-VATE 1022 trial and is in line with the population segment expected to receive inotuzumab in the the UK. HSCT is potentially curative, the model uses a time horizon of 60 years to ensure that all the costs and outcomes over a patient's full lifetime were captured in line with the NICE reference case.[140]

The model structure is shown in Figure 23. This model structure is reflective of the disease area where the goal is remission and HSCT, and is in line with the design of the INO-VATE 1022 study where two primary endpoints are remission (CR/CRi) and OS. The level of remission is the CR/CRi rate, as defined in Section 3.1 (Table 5). PFS was also captured within the trial, and is incorporated as a sub-state within the model.

Figure 22: Model structure diagram



Note: Patients can receive HSCT whether they are No CR/CRi or CR/CRi.
Key: CR, complete response; CRi, complete response with incomplete count recovery; SCT, stem cell transplant.

All patients enter the model in Cycle 0 (*baseline entry level*), where it is assumed that they have not begun treatment for R/R B-cell ALL and have therefore have not yet achieved treatment remission. By the end of the first cycle, Cycle 0, the model transitions patients from the *baseline entry level* into respective follow-on health states defined by their response to treatment and the presence (or absence) of subsequent HSCT, where they are for the beginning of their second cycle (Cycle 1). Assuming that patients' response to treatment is determined within 1 cycle is a simplification of reality, as in practice, it is possible for this to take slightly longer than 1 cycle. However, this simplifying assumption made by the model is broadly in line with the clinical trial, where the majority of patients who achieved CR/CRi had done so by Cycle 1 and [redacted] by Cycle 3. Indeed, UK clinical experts at a recent advisory board agreed that CR/CRi is typically detected in the first few cycles of treatment.[48] Furthermore, these clinicians considered that it would be uncommon to treat patients beyond 1 to 2 cycles, with a third cycle given as a maximum.

The transition in the first cycle to the respective states is done so by using probabilities derived from the results of the INO-VATE 1022 trial to determine the proportion of patients that achieve CR/CRi with no HSCT, the proportion of patients that would receive HSCT, and the patients that had No CR/CRi. These proportions (shown in Table 39) were used to inform the transitions from baseline into the respective health states at Cycle 1.

Table 39: Proportion of patients in each health state from Cycle 1

Health state	Inotuzumab	Standard of care
No CR/CRi	[redacted]	[redacted]
CR/CRi and no HSCT	[redacted]	[redacted]
HSCT & post-HSCT	[redacted]	[redacted]
Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant		

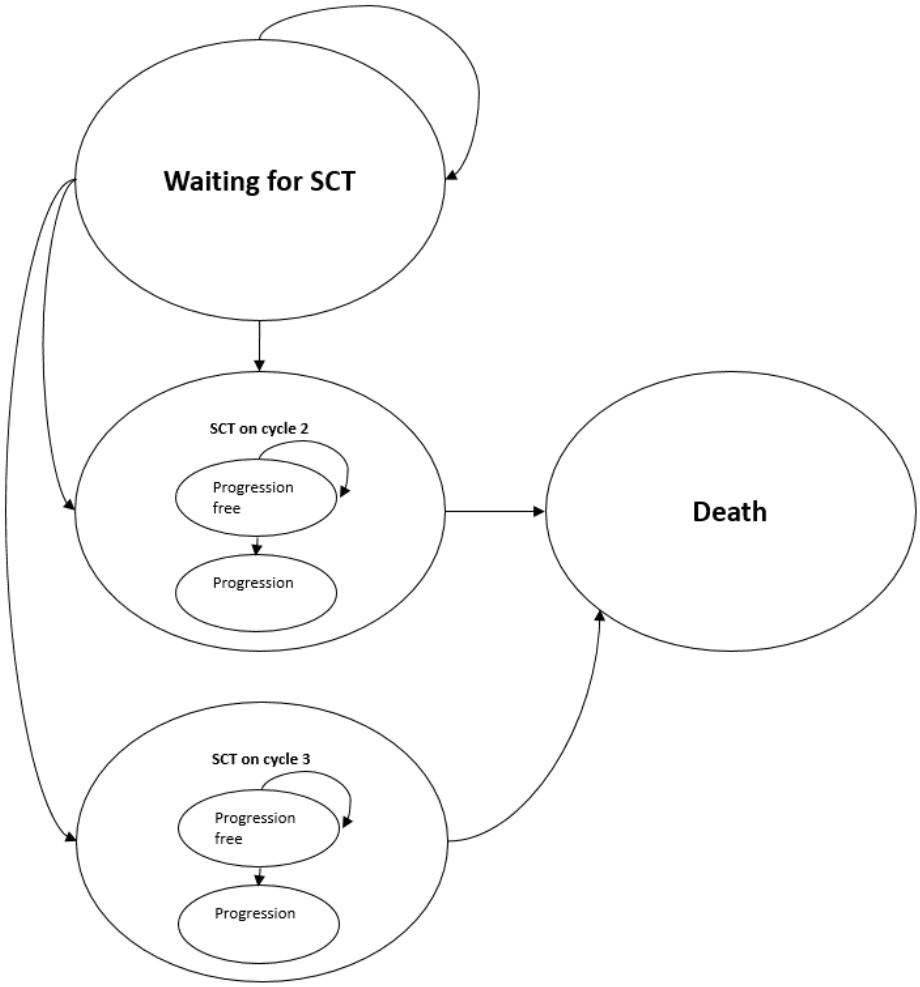
To best reflect the R/R B-cell ALL patient journey in practice and the transition to HSCT, tunnel states were developed to represent the wait that patients may experience while waiting for HSCT. Time to HSCT data were taken from the INO-VATE 1022 trial to determine how many cycles patients in the '*SCT & post-HSCT*' health state spend waiting in a holding state before their transplant. The proportions

of patients receiving HSCT from the trial is shown in Table 40. A diagrammatic example of the tunnel states is shown in Figure 24, using an example of HSCT across 2 cycles. Within each tunnel state, patients either stay progression free, progress or die. Within the trial, the patients waiting time to receive HSCT once eligible was up to [redacted] cycles for inotuzumab and [redacted] cycles for SoC. However, UK clinical experts at a recent advisory board[48] noted that time to HSCT is substantially shorter in UK clinical practice than within the clinical trial, with patients who go on to receiving HSCT typically doing so by the third cycle. As such, the model base case uses the trial data to inform the patients waiting for HSCT, and scenario analyses explores the cost-effectiveness by assuming a maximum of three cycles spent waiting for HSCT, in line with UK clinical practice (those in cycles 4-15 in Table 40 are moved forwards to cycle 3). To explore the impact of waiting for potentially curative therapy fully, a further scenario was conducted that uses the average time patients received a HSCT in the trial ([redacted] months for inotuzumab patients and [redacted] months for SoC patients on average, reflective of a maximum wait time of [redacted] and [redacted] cycles in the two arms).

Table 40: Proportion of HSCT patients receiving HSCT in each cycle

Cycle	Inotuzumab arm	SoC arm
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
Total	**100.00%**	**100.00%**

Figure 23: Example of the tunnel states used for the Post-HSCT health state



Key: SCT, stem cell transplant.

Once patients have transitioned to their respective health state (‘*No CR/CRi & no HSCT’, ‘CR/CRi and no HSCT’, ‘HSCT & post-HSCT’*), they are modelled based upon PFS and OS (where PFS and OS are reflective of whether patients receive a HSCT, and if not whether patients achieved CR/CRi). The time-dependent probability of progressing or dying are then informed using parametric survival curves as described in Section 5.3.

MRD negativity has been shown to be a key determinant of a patient’s prognosis for survival following HSCT[44, 46, 65, 142, 143]; therefore, its inclusion was considered relevant for the economic model. However, as acknowledged within the literature, there is considerable uncertainty about its applicability and value in a relapsed population.[44, 143] Furthermore, given all the parametric survival modelling considered

a treatment covariate, the benefit of increased MRD negativity for patients that received inotuzumab (see Section 4.7) would already be inherently captured within the analysis. Therefore, despite prior economic models in similar disease areas including MRD status within their model structure, the cost-effectiveness model built for this analysis did not include MRD status.[143] Nonetheless as MRD status is cited as an important prognostic factor for patient outcomes in R/R B-cell ALL[44, 46, 65], and there was a significant difference in the proportion of patients that achieved MRD negativity in the two treatment arms in the INO-VATE 1022 study (see Appendix 4), the inclusion of MRD was explored in sensitivity analysis. Within this scenario post-HSCT survival data was pooled, with parametric survival curves fit to the data that included a covariate adjustment for MRD status.

The main features of the model are reported in Table 41, with a model summary diagram presented in Figure 53. The model considered costs associated with treatment, administration, subsequent treatment, AEs, HSCT and end of life. The costs were split based upon the level of remission and occurrence of HSCT, and are described in detail in Section 2155.5.

HRQL is captured based on the health states within the model and dependent on the progression status of the patient. HRQL was expected to differ based upon remission status, progression, and time after HSCT. Utility decrements were applied for patients that experienced graft versus host disease (GvHD) and VOD, which are a direct result of HSCT, and therefore unlikely to be captured within the on-treatment utilities obtained from within the INO-VATE 1022 trial. However, this may be considered a conservative approach as some patients in the inotuzumab arm experienced VOD while on treatment, and these disutilities would already be reflected in the EQ-5D. The potential double counting of this disutility reduces the average QALYs for inotuzumab. HRQL is described in Section 5.4

Table 41: Features of the *de novo* analysis

Factor	Chosen values	Justification

Factor	Chosen values	Justification
Time horizon	60 years	Lifetime horizon as per NICE guidance[140], considered long-enough to capture the long-term economic and clinical aspects of R/R B-cell ALL with 100% of patients dying by the end of the time horizon
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case[140]
Base case range is presented with discounting reflecting of 1.5% and 3.5%	Yes	The Reference Case stipulates a discount rate of 3.5% for costs and benefits. However, bridging to HSCT can potentially restore patients to normal life expectancy. The NICE Methods Guide suggests a discount rate of 1.5% for benefits in cases where costs or benefits are sustained over a very long period (normally at least 30 years).[140, 144]
Perspective (NHS/PSS)	NHS England and Wales	NICE reference case[140]
Key: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.		

The key goal of treating R/R ALL (with inotuzumab or SoC) is to bridge to potentially curative therapy, with patients potentially benefitting from a return to normal life expectancy with an otherwise very aggressive, end-of-life disease. The majority of costs of treatment (drug acquisition costs and cost of HSCT in particular) are experienced in the short term; hence, discounting future costs produces a similar estimate for lifetime costs as no discounting. However, as benefits may be experienced in the longer run (i.e. a return to normal life expectancy), discounting future benefits provides a substantially lower estimate of lifetime benefits (QALYs) than no discounting. As such, the cost to benefit ratio, (the incremental cost-effectiveness ratio [ICER]) increases when discounting is applied. As a result, under these circumstances, discounting may potentially underestimate the value of a treatment in this disease area.[145] A NICE citizens council meeting in 2011 summarised that the likely scenario in which lower discounting rates would need to be explored should be where the majority of costs are accrued up front while the benefits are accrued over a life-time, producing 'high QALY benefit' or a total cure.[145]

The NICE Methods Guide (6.2.19) also discusses this phenomenon, stating that in cases when treatment restores people who would otherwise die or have a very

severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. To account for this, the Methods Guide advises using a discount rate of 1.5% for benefits, lower than the typical 3.5%. As this guidance is applicable to the treatments and disease pathway in question in this appraisal, the base case presents a range of ICERs which reflect costs and benefits discounted at the lower 1.5% as well as the typical 3.5%. Sensitivity analyses are also presented with 0% discounting which illustrate the true impact of future benefits.

5.2.3. Intervention technology and comparators

Inotuzumab is administered intravenously at a dose of 0.8mg/m^2 on Day 1, 0.5mg/m^2 on Day 8 and Day 15 in Cycle 1; 0.8mg/m^2 or 0.5mg/m^2 on Day 1, 0.5mg/m^2 on Day 8 and Day 15 in Cycle 2 and subsequent cycles. Cycle 1 is a 21-day cycle, or up to 28 days to recover from toxicity, and subsequent cycles are 28 days. Patients can receive this treatment for up to 6 cycles. Only those with CR/CRi and not going to HSCT would go beyond cycle 3.

The dosing of inotuzumab implemented within the model was in accordance with the administration schedule used within the INO-VATE 1022 study, although it should be noted a maximum of 3 cycles is expected to be recommended in the SPC; this is explored in a scenario analysis.

The comparators considered in this economic evaluation represent the current standard of care (SoC) for patients with R/R B-ALL in the UK, which is predominantly FLAG-based (fludarabine plus cytarabine plus G-CSF) combination chemotherapy. FLAG-based combination chemotherapy reflects both feedback from clinicians and the available literature commenting on treatment practices[95], which indicate that FLAG-based regimens are established clinical practice in the UK for the majority of adults with R/R B-ALL; this is also in line with the final scope. However, expert clinical opinion indicates treatment decisions are commonly made at the individual patient level.[48] The most robust evidence base available for the comparison between inotuzumab and a FLAG-based regimen is from the INO-VATE 1022 trial. Patients in the investigator's choice arm within the trial received one of three possible treatments; FLAG, CM, or HIDAC. Approximately [redacted] of patients in the INO-VATE 1022 trial received FLAG. CM and HIDAC have also been included in

the SoC treatments in the model, based on the proportion of patients in the trial who received these regimens ([redacted], respectively). Therefore, the INO-VATE 1022 investigators choice arm of the trial is used to inform the SoC arm within the economic model. Regarding FLAG, the addition of idarubicin (FLAG-IDA) which is another treatment regimen administered in a UK setting, has also been explored within the economic evaluation. Throughout the base case the efficacy observed for FLAG is used as a proxy for FLAG-IDA. As there is little evidence available within the literature to suggest that there is any difference in the efficacy of FLAG-IDA versus FLAG due to the addition of idarubicin, the model makes the assumption that the two have equivalent efficacy. This is supported by a small study of 105 patients with poor risk acute leukaemia or myelodysplastic syndrome that were treated over a 4-year period and showed no statistical difference in outcomes between FLAG and FLAG-IDA.[96]

Tyrosine kinase inhibitors (TKIs) have been included as a comparator for Ph+ patients in combination with the chemotherapy selected as SoC in line with the final scope shown in Table 1. There is uncertainty how effective TKIs are after further lines of treatment, and there are limited efficacy data to inform the model; therefore, only the costs of TKIs have been incorporated for these patients, and efficacy remains the same as SoC.

Clofarabine was identified as a treatment for some R/R B-ALL patients within the NICE scope; however, as noted in Pfizer comments made during the scoping process, it is not a relevant comparator for this appraisal. Clofarabine is licenced for patients up to age 21, with the SPC stating that there are insufficient data to establish safety and efficacy in adult patients.[146] Key clinician expert opinion has indicated that clofarabine is used off-label in an estimated 10–15% of 18–30 year olds in the UK. As this use is off-label, it is not appropriate to compare to inotuzumab within this submission. Furthermore, with under 30s likely to constitute less than 30% of the expected eligible population, clofarabine usage would equate to less than 5% of the whole adult population. Therefore, as it is not the standard of care relevant to this decision problem, it has not been considered a comparator in the economic evaluation.

SoC posology is summarised in Table 42, within the economic model the dosage considered for the cost of SoC treatments is based on the actual dosage received per cycle by the patients in the INO-VATE 1022 trial.[75]

Table 42: Dosing schedule for inotuzumab and comparators

Regimen		Dosage	Stopping rules	Source
Inotuzumab		Cycle 1 (21 days) 0.8mg/m^2 on Day 1, 0.5mg/m^2 on Day 8 and 0.5mg/m^2 Day 15. Cycle 2+ (28 days) 0.8mg/m^2 or 0.5mg/m^2 on Day 1, 0.5mg/m^2 on Day 8 and 0.5mg/m^2 Day 15.	Up to 6 cycles	INO-VATE 1022 CSR[3]
FLAG	Fludarabine	30mg/m^2 for 5 consecutive days per 28-day cycle	Up to 4 cycles	
	Cytarabine	2g/m^2 for 6 consecutive days per 28-day cycle		
	G-CSF	5µg/kg per day		
CM	Cytarabine	200mg/m^2 for 7 consecutive days per 15–20-day cycle	Up to 4 cycles	
	Mitoxantrone	12mg/m^2 for 3 consecutive days per 15–20-day cycle		
HIDAC		3g/m^2 every 12 hours	Up to 12 doses	
TKI (Imatinib)		600mg per day orally	Disease progression	SPC[147]

Key: CM, cytarabine plus mitoxantrone; CSR, clinical study report; FLAG, fludarabine, cytarabine, granulocyte-colony stimulating factor; G-CSF, granulocyte colony-stimulating factor; HIDAC, high dose cytarabine; SPC, summary of product characteristics; TKI, tyrosine kinase inhibitor.

SoC in the model considered a combination of FLAG, CM and HIDAC, which was administered within the INO-VATE 1022 trial. At a recent UK advisory board, clinical experts were presented with the data from the INO-VATE 1022 study, and asked to comment on the investigators choice arm with regard to the split of the treatments administered (as presented in Table 43) and the overall outcomes. The clinicians

considered that the clinical outcomes observed, along with the majority of patients receiving FLAG, were representative of the current standard of care within the UK. Within the base case, a blended comparison based on the INO-VATE 1022 study is used to estimate a weighted treatment cost. In scenario analyses, each comparator is explored individually (retaining the efficacy of the treatment mix from the trial, but applies 100% of the respective treatment costs, respectively).

Table 43: Estimated proportion of patients receiving each of the treatments that form standard of care obtained from the INO-VATE 1022 trial

Treatment	Proportion
FLAG	[redacted]
CM	[redacted]
HIDAC	[redacted]
Key: CM, cytarabine plus mitoxantrone; FLAG, fludarabine, cytarabine, granulocyte-colony stimulating factor; HIDAC, high dose cytarabine.	

5.3 Clinical parameters and variables

Clinical data were obtained from the Phase III RCT, INO-VATE 1022, described in Section 0. Patients were assigned in a 1:1 ratio to either receive inotuzumab or the investigator's choice of standard therapy (FLAG, CM or HIDAC). Data obtained from the trial that are used in the model are summarised in Table 44.

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Table 44: Application of clinical trial data within the model

Data	Application in the model

Data	Application in the model
PFS	Used to fit parametric survival curves to extrapolate long-term PFS estimates.
OS	Used to fit parametric survival curves to extrapolate long-term OS estimates.
Time to HSCT	Informs how many patients receive an HSCT per cycle.
Utilities on treatment	Used to inform the utility of progression-free patients in the No CR/CRi & no HSCT and CR/CRi & no HSCT health states for each arm while on treatment.
Adverse event incidence	Informs the proportion of patients who experienced an adverse event and associated cost in each arm.
BSA	Used to calculate drug costs based on average dose received per cycle.
Weight	Used to calculate drug costs based on average dose received per cycle.
Proportion of patients who had subsequent treatment	Used to calculate the cost of subsequent treatments in both arms.
Key: BSA, body surface area; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival; PFS, progression-free survival; HSCT, stem cell transplant.	

5.3.1. Efficacy data

Within the model, efficacy data were obtained from the INO-VATE 1022 trial using the ITT data outlined in Section 4. These were used to inform both the intervention and comparator arms. In the Investigator's choice arm, [redacted] out of the 164 patients were randomised but were untreated. To limit the chance of bias towards the inotuzumab arm, given that these patients would be categorised as not achieving CR/CRi, these [redacted] patients have been excluded from the analysis and only the safety population is considered. This approach is conservative compared to the ITT analysis as the [redacted] patients would otherwise be considered as patients in the No CR/CRi health state, and therefore would rebalance the proportion of patients in each health state, such that the SoC arm would have fewer patients in HSCT and CR/CRi. Removing these patients provides a more accurate representation of the efficacy of SoC arm used to inform the economic model. The overall PFS and OS efficacy data from the inotuzumab is the same as that reported in Section 4 (Figure 8 and Figure 9). The PFS and OS from efficacy data from the INO-VATE 1022 trial for the patients that were treated (removing the [redacted] untreated patients) in the

investigators choice arm, used to inform the SoC arm within the model, are reported in Figure 25.

Figure 24: INO-VATE 1022 SoC safety population: PFS and OS

Key: OS, overall survival; PFS, progression-free survival; SoC, standard of care.

Based on feedback from UK clinicians, the efficacy of the comparator arm within the INO-VATE 1022 trial was assumed to be equivalent to that expected within UK clinical practice.[48]

As outlined in Section 5.2.2, the cost-effectiveness model considered three major health states, patients who did not achieve a response (*No CR/CRi & no HSCT*), patients who achieved a response but did not go on to have an HSCT (*CR/CRi & no HSCT*), and patients who underwent HSCT (*SCT & post-HSCT*).

For the outcomes of OS and PFS covariate adjusted parametric survival models (PSM) were fitted. PSMs were fitted respectively to patients from the following three states:

- Non-responders (*No CR/CRi & no HSCT*)
- Responder with no stem cell transplant (*CR/CRi & no HSCT*)
- Patients who receive HSCT (*HSCT & post HSCT*)

Table 39 reports the proportion of patients in each of the two model arms (inotuzumab and SoC), within each state.

For the first two categories '*No CR/CRi & no HSCT' and 'CR/CRi & no HSCT'*, PSMs were fitted using the date of randomisation as the baseline. For patients receiving HSCTs, PSM were fitted from a baseline of the date of HSCT.

Covariate analysis was conducted with the intention of being able to explore the impact of different prognostic factors in the R/R B-cell ALL population. Justification for the covariates selection is provided in Table 45 and the covariates were also validated by UK clinicians at a recent advisory board.[48]

Table 45: Covariates and justifications

Covariate	Justification
Treatment	Treatment covariates were incorporated within the model to allow the shape and scale parameters to vary in accordance to the specific treatment data
Age group (<55/≥55)	This was a stratification factor in the INO-VATE 1022 trial
Duration of first remission at randomisation IVRS (< 12 months, ≥ 12 months)	This was a stratification factor in the INO-VATE 1022 trial
Salvage status (1/2) IVRS	This was a stratification factor in the INO-VATE 1022 trial
Philadelphia category (Ph+/-)	Given the importance of Ph status for prognosis, the parametric models included this covariate to explore the performance of inotuzumab versus SoC within the population
Prior HSCT (Yes/No)	Included to be in line with current UK clinical practice where a 2nd SCT is not reimbursed. Also, in current clinical practice, FLAG-IDA would be prescribed for patients with the aim of bringing them to SCT. A patient with a prior SCT, would therefore not be treated with FLAG-IDA, as a second SCT would not be reimbursed.
Region (EU, North America, Japan and Other Asia)	Treatment in Japanese patients were seen as an outlier from other countries, with regard to the typical conditioning regimens available (such as ThioTEPA associated with an increase in the incidence of VOD), and therefore was incorporated as a covariate to explore its impact on the predicted cost-effectiveness outcomes.
Key: HSCT, haematopoietic stem cell transplant; IVRA, interactive voice response system; Ph+/-, Philadelphia chromosome positive/negative; SoC, standard of care; VOD, veno-occlusive liver disease.	

All covariate parameters are presented in Appendix 5. The covariate PSMs were stratified by treatment while keeping the remaining covariate coefficients constant. Models fitted include:

- Exponential
- Weibull
- Log normal
- Log logistic
- Gompertz
- Generalised gamma

The best-fitting parametric curves were identified through visual inspection, assessment of clinical plausibility, and the typical metrics of statistical fit (Akaike information criterion (AIC) scores and Bayesian information criterion (BIC) scores) in line with the NICE Decision Support Unit guidelines.[148] Throughout the analysis the treatment covariate is applied such that there is a treatment effect on both the shape and the scale parameter, therefore the curve can change accordingly to fit the data more accurately than a standard HR. This is applied to all parametric curves apart from the exponential, as there is only one parameter (the scale parameter) used to inform survival in this case.

It is worth noting that within the trial, two definitions of PFS were captured. Outcomes relating to the ‘standard’ definition of PFS more commonly used in solid tumour oncology which defines PFS as the time from randomisation to the first documentation of disease progression or death due to any cause, whichever occurs first. In haematology-oncology, PFS is typically defined more extensively to include not only the time from randomisation to the first documentation of disease progression or due to death, but also disease progression incorporates objective progression, as well as relapse from CR/CRi, and treatment discontinuation due to the global deterioration of health status. This definition of PFS also includes starting new induction therapy or post-therapy SCT without achieving CR/CRi. Both of these measures were included in the trial, but because the latter is considered more relevant to clinical practice in ALL, it is this definition which has been used to inform the PFS states within the economic evaluation

5.3.2. No CR/CRi & no HSCT

Patients in the No CR/CRi & no HSCT category had the poorest outcomes, with the shortest survival times based upon the extrapolated PFS and OS curves. In total, there were [redacted] patients in the inotuzumab arm compared to [redacted] in the investigator's choice arm. As stated in Section 5.2.3, investigator's choice was used as a proxy for SoC within the model. No statistical difference was found between inotuzumab and SoC in the PFS and OS curves shown in Figure 26 and Figure 27.

Figure 25: PFS in No CR/CRi & no HSCT patients

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; PFS, progression-free survival; SoC, standard of care.

Figure 26: OS in No CR/CRi & no HSCT patients

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival; SoC, standard of care.

5.3.2.1. No CR/CRi & no HSCT - progression free survival

Parametric survival curves were fitted to the data for patients who were categorised as No CR/CRi who did not undergo an HSCT. Parametric curves and Kaplan–Meier data are shown in Figure 28 and Figure 29 for inotuzumab and SoC respectively.

Figure 27: No CR/CRi & no HSCT parametric PFS curves – inotuzumab

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 28: No CR/CRi & no HSCT parametric PFS curves – SoC

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care.

The AIC and BIC statistics are presented in Table 46. The log-logistic curve was selected due to it being the best statistical fit (as defined by the AIC and BIC criteria) and the goodness of visual fit.

Table 46: AIC and BIC statistics: No CR/CRi & no HSCT PFS

Parametric curve	AIC	BIC
Log-logistic	1031.88	1065.13
Log-normal	1039.40	1072.65
Generalised Gamma	1041.40	1077.42
Weibull	1058.59	1091.84
Gompertz	1070.48	1103.73
Exponential	1092.79	1128.71

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival.

5.3.2.2. No CR/CRi & no HSCT - overall survival

For OS the parametric curves and Kaplan–Meier data are shown below in Figure 30 and Figure 31 for inotuzumab and SoC, respectively.

Figure 29: No CR/CRi & no HSCT parametric OS curves – inotuzumab

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; OS, overall survival.

Figure 30: No CR/CRi & no HSCT parametric OS curves – SoC

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; Kaplan–Meier; OS, overall survival; SoC, standard of care.

The AIC and BIC statistics are presented in Table 47. As with PFS, the log-logistic curve was selected due to it being one of the best statistical fits (as defined by the AIC and BIC criteria) and the goodness of visual fit.

Table 47: AIC and BIC statistics – No CR/CRi & no HSCT OS

Parametric curve	AIC	BIC
Log-normal	1307.72	1340.97
Generalised Gamma	1308.19	1344.21
Log-logistic	1308.98	1342.23
Weibull	1311.19	1344.44
Gompertz	1321.52	1354.77
Exponential	1332.67	1368.58
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival.		

5.3.3. CR/CRi & no HSCT

In clinical practice, despite patients achieving CR/CRi, some patients will not undergo HSCT. There are a multitude of reasons for this, including lack of a compatible donor, other health complications, patient preference, and expected poor prognosis post-HSCT. Although not statistically significant, there is a clear favourable PFS outcome in inotuzumab over the SoC arm (Figure 32), despite these patients not going on to receive curative therapy. The OS curves for these patients are displayed in Figure 33, showing no difference in expected outcomes between the two treatment arms and similar median survival (see Section 4); this aligns with expectation, as the benefit of inotuzumab compared to SoC is to bridge more patients to potentially curative therapy (and thus potentially longer OS). Among those patients who have not gone on to receive HSCT, the lack of OS benefit is therefore expected. Within the model [redacted] of inotuzumab patients were in the '*CR/CRi & no HSCT'* health state, and [redacted] in the SoC arm [redacted].

Figure 31: PFS in CR/CRi & no HSCT patients

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; PFS, progression-free survival; SCT, stem cell transplant; SoC, standard of care.

Figure 32: OS in CR/CRi & no HSCT patients

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival; SCT, stem cell transplant; SoC, standard of care.

5.3.3.1. CR/CRi & no HSCT - progression free survival

Parametric survival curves were fitted to the data for patients who were categorised as CR/CRi patients who did not undergo an HSCT. The AIC/BIC statistics are reported in Table 48. The log-normal curve was considered the best statistical fit with the lowest AIC and BIC statistics. The Gompertz and exponential curves were excluded due to the poor visual fits to the Kaplan–Meier data, particularly in the initial 40% of the survival distribution for inotuzumab. Among the remaining distributions there were minimal differences, with all being potentially clinically plausible; this plausibility is based upon an expected limited tail in the group who do not go on to HSCT, as a benefit of potentially curative therapy is not present. Applying this rationale to both the inotuzumab and SoC curve selection, and considering statistical fit, the log-normal was selected.

Figure 33: PFS CR/CRi & no HSCT – inotuzumab

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SCT, stem cell transplant.

Figure 34: PFS CR/CRi & no HSCT – SoC

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SCT, stem cell transplant; SoC, standard of care.

Table 48: AIC and BIC statistics: PFS CR/CRi & No HSCT

Parametric curve	AIC	BIC
Log-normal	827.7401	856.3245
Generalised Gamma	829.7389	860.7052
Log-logistic	829.9088	858.4931
Weibull	834.6307	863.215
Gompertz	850.1777	878.762
Exponential	888.3582	918.0503
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival.		

5.3.3.2. CR/CRi & no HSCT - overall survival

Parametric survival curves were fit to the OS data for patients who were categorised as CR/CRi patients who did not undergo an HSCT (Figure 36 and Figure 37). The AIC/BIC statistics are reported in Table 49. The log-logistic curve was considered the best statistical fit with the lowest AIC and BIC statistics. The log-logistic curves were selected for this category of patients due to good statistical fit, visual fit and clinical plausibility. The distributions for the two arms are similar, which is in line with the similarities seen in the Kaplan–Meier plots. It should be noted, however, that the choice of the log-logistic favours SoC in the tail of the curve, in contrast to the Kaplan–Meier data which favour inotuzumab; as such, use of these distributions produces a conservative estimate of inotuzumab's survival benefit.

Figure 35: OS CR/CRi & no HSCT – Inotuzumab

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; OS, overall survival; SCT, stem cell transplant.

Figure 36: OS CR/CRi & no HSCT – SoC

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; OS, overall survival; SCT, stem cell transplant; SoC, standard of care.

Table 49: AIC and BIC statistics: OS CR/CRi & No HSCT

Parametric curve	AIC	BIC
Log-logistic	892.24	920.82
Log-normal	893.19	921.78
Generalised Gamma	895.05	926.02
Weibull	899.07	927.65
Gompertz	912.47	941.06
Exponential	932.54	962.23
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival.		

5.3.4. SCT & Post-HSCT

Within the INO-VATE 1022 trial there was a statistically significant difference in the proportion of patients who underwent HSCT in the inotuzumab arm [redacted] compared to the investigator's choice arm of the trial [redacted] with p<0.0001. As described in previous sections, the value of inotuzumab is that it allows patients to

reach CR/CRi, and acts as a bridge to potentially curative therapy, which is HSCT in the model, but it is expected other curative therapies may become available. Given that HSCT is the only potentially curative treatment available currently for patients with ALL, it is a vital element in the treatment pathway and important for overall outcomes of the ALL patient, particularly in the R/R setting where often patients' treatment options are limited and their health rapidly declining.

It is worth noting that the economic model considers the total number of patients within the safety dataset that had an HSCT, regardless of their remission status, and regardless of their time of transplant and whether this was received prior to any post-induction therapy. All HSCT rates and outcomes are included to ensure that the economic model is reflective of what was observed within the trial, to avoid any potential misinterpretation of the outcomes. Table 50 reports the number and proportion of patients who received HSCT in the trial, between the first dose of treatment date to the start of post-induction therapy. As shown, [redacted] of patients [redacted] in the inotuzumab arm but only [redacted] in the investigator's choice arm received their HSCT prior to any post induction therapy. This indicates that there is potential risk of overestimating the number of patients who receive HSCT as a direct result of SoC within the model, given a large proportion of patients instead may have had the HSCT as a result of response to a subsequent induction treatment. The approach taken within the model is therefore conservative in the benefits that inotuzumab may offer in comparison to the SoC. As noted in Section 5.5.6, costs associated with subsequent therapy, which may have allowed patients to proceed to HSCT, were captured within the economic model to also be reflective of the INO-VATE 1022 study.

Table 50: Comparison on HSCT rates based on post induction therapy

	Inotuzumab[n=164](%)	**Investigator's choice [n=[redacted]](%)**
Number of patients with HSCT between the first dose date to start of post induction therapy	[redacted]	[redacted]
Number of patients with HSCT in safety population	[redacted]	[redacted]

Patients who underwent HSCT had the best outcomes, with the longest survival times based upon the extrapolated PFS and OS curves. All curves were fit to the data from the point of HSCT. Figure 38 and Figure 39 report the PFS and OS in the post-HSCT health state, respectively. As shown, the curves cross in both instances, and therefore the assumption of proportional hazards and the use of a HR is not appropriate. Instead we add the treatment covariate such that there is a treatment effect on both the shape and the scale parameter, therefore the curve can change accordingly to fit the data more accurately than a standard HR.

Within this health state, due to the lack of proportional hazards, the use of median survival time when assessing the data are not applicable in this setting as it does not provide context for absolute risk and treatment benefit. Further to that, median survival estimates only capture the first 50% of the population, which may not be applicable in the post-HSCT setting, where patients often experience high rates of mortality following the surgery. However, after this period of mortality risk, patients often experience far better survival. Therefore, the use of medians to explore survival is limited in this setting (see Section 4 where this is discussed and RMST is conducted as an alternative summary measurement). For the post-HSCT analysis, it is imperative to look at the entire survival captured within the trial.

Further to the benefit of allowing more patients to receive potentially curative therapy, the Kaplan–Meier plots indicated that those in the inotuzumab arm also benefited more post-HSCT than those post-HSCT in the SoC arm, in the longer-term (post 2 years). A potential explanation for this is the higher rate of MRD-negativity in inotuzumab patients receiving HSCT versus SoC ([redacted]% vs [redacted]%), as MRD-negativity has previously been found to be a factor in determining a patients' long-term survival.

Figure 37: PFS in HSCT & Post-HSCT patients

Key: PFS, progression-free survival; SCT, stem cell transplant; SoC, standard of care.

Figure 38: OS in HSCT & Post-HSCT patients

Key: OS, overall survival; SCT, stem cell transplant; SoC, standard of care.

5.3.4.1. Time to HSCT

Time to HSCT is modelled through tunnel states and described in Section 5.2.2. The data used are informed by the INO-VATE 1022 trial and presented in Table 40.

5.3.4.2. Post-HSCT progression free survival

Parametric survival curves were fitted to the data for patients who incurred a HSCT. The AIC/BIC statistics are reported in Table 48. The generalised gamma, log-normal and exponential curves were not considered appropriate fits to the data by visual inspection and are therefore not included in curves presented Figure 40 and Figure 41. These are reported in Appendix 6. Due to treatment being included as a covariate, the same parametric curve was selected for both arms. Based on visual inspection and clinical plausibility, the Gompertz curve was selected for use in the base case.

Figure 39: PFS post-HSCT InO: Parametric curves - inotuzumab

Key: PFS, progression-free survival; SCT, stem cell transplant.

Figure 40: PFS post-HSCT SoC: Parametric curves - SoC

Key: PFS, progression-free survival; SCT, stem cell transplant; SoC standard of care.

Table 51: AIC and BIC statistics: PFS post-HSCT

Parametric curve	AIC	BIC
Generalised Gamma	628.84	658.61
Weibull	648.62	676.10
Exponential	650.86	673.73
Gompertz	651.75	679.24
Log-logistic	653.16	680.65
Log-normal	655.48	682.96

5.3.4.3. Post-HSCT overall survival

Parametric survival curves were fitted to the data for patients who were categorised as patients who incurred a HSCT. Potentially curative therapy, such as HSCT, affords patients the best chance at long term survival. The trial data clearly show a demonstrative benefit in the tail for inotuzumab, illustrated in the Kaplan–Meier plot, as a consequence of more patients reaching HSCT**.** Due to treatment being included as a covariate, the same parametric curve was selected for both arms, the Gompertz curve was selected as the base case post-HSCT curve. Not only was the Gompertz

curve the best statistical fit to the Kaplan–Meier data (as shown in Table 52), but it was also a good visual fit to both comparators up to the “cure point” of 3 years. Patients can be expected to return to normal life expectancy 2 to 5 years post-HSCT, as they are deemed to have reached a “cure point” (see Section 5.3.5). Thus, the Gompertz was the only parametric curve that was feasible for use due to the poor fit of the others to the inotuzumab Kaplan–Meier data.

Figure 41: OS post-HSCT: Parametric curves - Inotuzumab

Key: OS, overall survival; SCT, stem cell transplant.

Figure 42: OS post-HSCT SoC: Parametric curves – SoC

Key: OS, overall survival; SCT, stem cell transplant; SoC, standard of care.

Table 52: AIC and BIC statistics: OS Post-HSCT

Parametric curve	AIC	BIC
Gompertz	947.05	979.35
Log-normal	953.43	985.72
Generalised Gamma	953.95	988.93
Log-logistic	956.10	988.39
Exponential	957.44	990.26
Weibull	960.46	992.76

5.3.4.4. Pooled survival post-HSCT

Given the limited data available, a scenario analysis was also performed that explored cost effectiveness results assuming that the survival post-HSCT was independent of treatment. Within this scenario, the data from inotuzumab and SoC were pooled and parametric curves were fitted to the data. The survival curves had one covariate adjusting for difference between the arms that was applied based on the rate of MRD negativity achieved, which is an important prognostic factor of survival post-HSCT.[44, 46, 65] More details of this scenario are provided in Appendix 7.

5.3.5. Cure post-HSCT

Within the '*HSCT & Post-HSCT'* health state, the model makes the simplifying assumption that patients achieve a 'cure' after HSCT if they are still alive beyond 3 years. Previous economic models in the same and similar therapeutic areas had used an estimate of up to 5 years after which patients still alive would 'return' to normal population life expectancy.[137, 143, 149], with estimates in the wider literature ranging from 1 year to 10 years.[143, 150, 151] UK clinical expert opinion agreed that patients surviving past a certain time post-HSCT could then be expected to experience normal life expectancy (a "cure"), with general consensus on a range of 2 to 5 years.

The model uses the parametric curves to fit survival up to the chosen cure point, beyond which it is assumed that patients' OS is denoted by general population mortality estimates (i.e. returning to normal life expectancy, a 'cure'). PFS remains stable post-HSCT but is capped by OS such that there can never be more patients in PFS than alive. To be most applicable to the UK population, the general population mortality estimates were calculated from the Office of National Statistics data[102] beyond the cure point, and adjusted for age and gender (which were matched to the baseline characteristics of the model reported in Section 5.2.1). General population mortality estimates are shown in Figure 44.

As outlined previously, the Gompertz was the only parametric curve that was considered for selection for post-SCT OS due to the poor fit of the others to the inotuzumab Kaplan–Meier data. Cure points ranging from 2 to 5 years were considered and the validity of each was discussed with a leading UK clinical expert. This validation focussed not only on what would be considered a reasonable time point to assume a return to normal life expectancy can be modelled, but which time point gave the most plausible estimates of longer term survival in the model. This is important because all parametric curves fit to SoC post-SCT OS render limited longer term survival benefit from HSCT (Figure 41), which is not reflective of clinical practice.

Using the Gompertz parametric curve with a 5 year cure point resulted in [redacted] of inotuzumab post-HSCT patients alive at this point while [redacted] of SoC patients

were. The proportion of patients still alive in the SoC arm under this parametric model was too few versus what is observed in UK clinical practice.

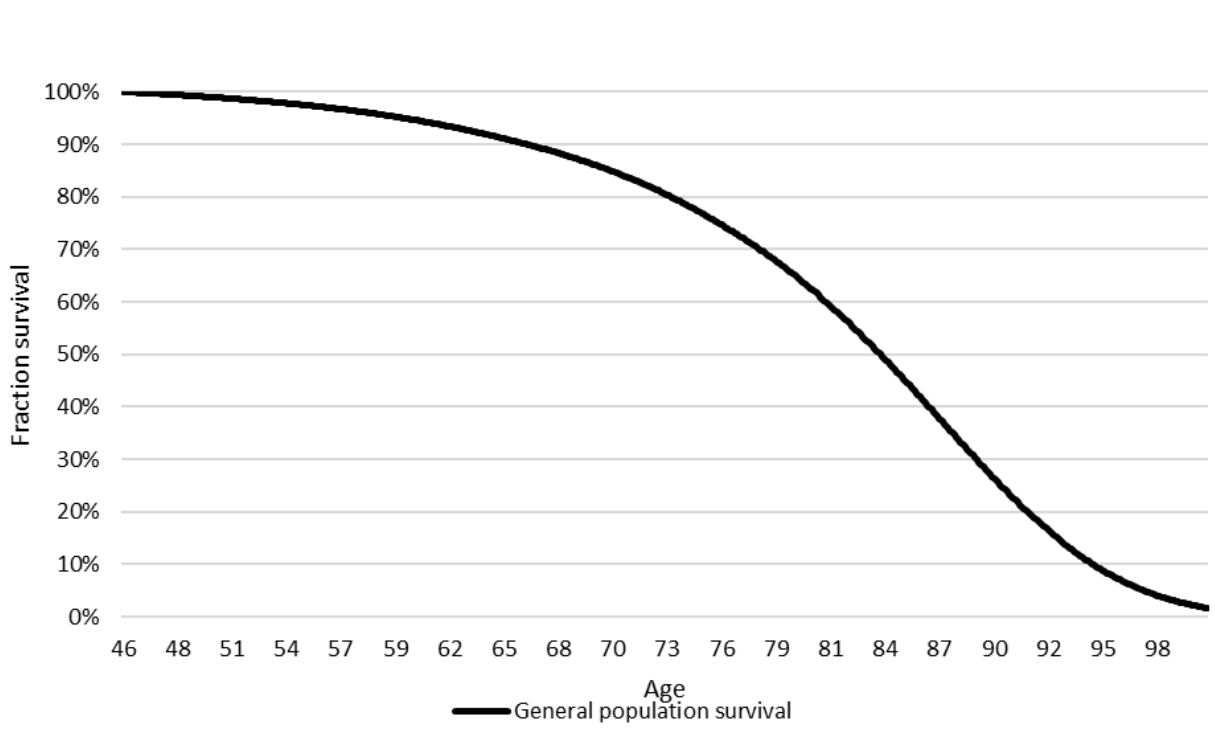
Using a cure point of 4 years resulted in a similar issue with only [redacted] patients alive at in the SoC arm.

A cure point of 2 years after HSCT was also considered, although these estimates were considered too conservative to inotuzumab given the benefit of inotuzumab post-HSCT and the increase in MRD negativity achieved with inotuzumab (resulted in [redacted] of patients alive in the inotuzumab post-HSCT arm and [redacted] in the SoC arm at the 2 year cure point).

The survival at 3 years ([redacted] for inotuzumab and [redacted] for SoC), although again conservative to the inotuzumab arm in comparison to the greater proportion of patients receiving transplant, was considered most clinically plausible, and therefore considered the most appropriate time for the cure point to be applied.

Further, the clinical expert agreed the choice of the three year cure point provides a good visual fit to the raw Kaplan–Meier data, including a more appropriate longer term estimate of OS for SoC than what was observed without the cure point in Figure 41.

Figure 43: General population overall mortality



The base case parametric PFS and OS curves are shown in Figure 45 and Figure 46, respectively, over the longer-term when the cure point is applied for post-HSCT patients. As shown by the curves, inotuzumab is anticipated to provide substantially longer survival in patients that receive HSCT.

Figure 44: PFS post-HSCT: Modelled outcomes

Key:PFS, progression-free survival; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Figure 45: OS post-HSCT: Modelled outcomes

Key: OS, overall survival; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

5.3.6. Modelled outcomes

The data and curves outlined in the previous Sections 5.3.2, 5.3.3 & 5.3.4 are applied within the model to the relevant proportion of patients in each health states within the two arms (Table 39). Figure 47 and Figure 48 shows the observed Kaplan–Meier data for PFS from the trial compared to the modelled PFS survival.

Figure 49 and Figure 50 shows the observed Kaplan–Meier data for OS from the trial compared to the modelled OS survival.

Figure 46: PFS – observed versus modelled outcomes (10 year time-frame)

Figure 47: PFS – observed versus modelled outcomes (60 year time-frame)

Figure 48: OS – observed versus modelled outcomes (10-year time-frame)

Figure 49: OS – observed versus modelled outcomes (60-year time-frame)

5.4 Measurement and valuation of health effects

5.4.1. Health-related quality-of-life data from clinical trials

As noted in Section 4.7 HRQL was measured in the INO-VATE 1022 trial using EORTC QLQ-C30, version 3.0[152], and the EQ-5D three-level version.[153] Patients in each arm completed the self-administered questionnaires at baseline (Cycle 1, Day 1) pre-dose, Day 1 at subsequent cycles, and at the end of treatment (either when the patient completed or discontinued treatment). They were completed prior to having any tests or any discussions with their physician or other health care professional.

The model uses the treatment specific EQ-5D utilities applied to the No CR/CRI & no HSCT and CR/CRi & no HSCT health states in the base case. The use of pooled utilities using the trial data is explored in scenario analysis.

The clinical study reports EQ-5D data based on the US value set as per the INO-VATE 1022 trial protocol. For this economic evaluation, the UK utility values have been calculated based on the EQ-5D UK value set in line with the NHS reference case and are shown in Table 53.[140] All HRQL values used within the model are outlined in Section 5.4.5.

Table 53: HRQL data from the INO-VATE 1022 trial

Health state	InO			SoC		
	N	Observations n (%)	Utility (95% CI)	N	Observations n (%)	Utility (95% CI)
Baseline (treatment specific)	164	150 (91.5%)	0.69 (0.65–0.74)	162	115 (71.0%)	0.67 (0.62–0.73)
Baseline (pooled)	326	265 (81.3%)	0.69 (0.65–0.72)			
No CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No CR/CRi & no HSCT (pooled)	[redacted]	[redacted]	[redacted]			
CR/CRi & no HSCT (pooled)	[redacted]	[redacted]	[redacted]			

Key: CI, confidence interval; CR, complete response; CRi, complete response with incomplete count recovery; HRQL, health-related quality of life; InO, inotuzumab ozogamicin; HSCT, haematopoietic stem cell transplant.

5.4.2. Mapping

No mapping was conducted within this analysis.

5.4.3. Health-related quality-of-life studies

5.4.3.1. Identification of studies

To inform the utility estimates that are used in the model, a SLR was performed to identify published utility values/HRQL associated with R/R ALL and associated treatments. All searches were conducted between 5 and 6 September 2016.

The full search strategies used in the electronic searches are provided in full in Appendix 8. The same databases, conference proceedings and the HTA websites as the cost-effectiveness SLR reported in Section 5.1 were searched for the HRQL SLR. Search strategies were designed using filters validated by SIGN, and all relevant studies in English were included (note: no relevant non-English language articles were identified at the screening stage).

No date restriction was applied to the utility searches due to the scarcity of utility/HRQL evidence for R/R ALL. No date restriction was applied to the utility searches due to the scarcity of utility/HRQL evidence for R/R ALL.

5.4.3.2. Study selection criteria

The detailed inclusion/exclusion criteria for utility studies are presented in Table 54. Studies that assessed mixed disease populations (e.g. R/R ALL and treatment-naïve ALL or R/R ALL and other malignancy/ies) were included only if separate data were reported for R/R ALL. Similarly, studies that assessed both paediatric and adult patients were planned to be included only if subgroup data were available for patients >15 years of age; none of such studies were identified. Economic evaluations as well as clinical studies reporting utility/HRQL values were included in the SLR. Letters and citations without an abstract were not included. Studies reporting utility values for non-treated patients were also included

Table 54: Inclusion and exclusion criteria for utility studies

Criteria	Inclusion	Exclusion
Population	Patients aged at least 15 years[a] Patients diagnosed with R/R ALL	Paediatric patients Patients with newly diagnosed ALL
Intervention/ comparator	No restriction	Studies were not excluded based on intervention or comparator therapy
Outcomes	Utility values Disutility values HRQL score	No restriction
Study types	Economic evaluations reporting utility/HRQL RCTs and observational studies reporting utility data Studies that provided extractable results Systematic review[b]	Non-systematic reviews, letters, comments or editorials
Language	Studies published in English Studies published in non-English languages were included and flagged[c]	Studies were not excluded based on publication language
Country	Study inclusion was not restricted to any specific country/region	

Key: ALL, acute lymphoblastic leukaemia; HRQL, health-related quality of life; RCT, randomised controlled trials; R/R, relapsed/refractory.
Notes: [a] Patients who were ≥15 years were included for completion as in R/R ALL they may treated with the treatment regimens recommended for adults; [b] Systematic reviews were included and flagged for bibliography searches; [c] Studies published in languages other than English were to be explored

Criteria	Inclusion	Exclusion
only if sufficient evidence was not identified from English language studies.		

Each reference (title and abstract) was independently reviewed by one reviewer by applying the basic selection criterion specified in Table 54. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

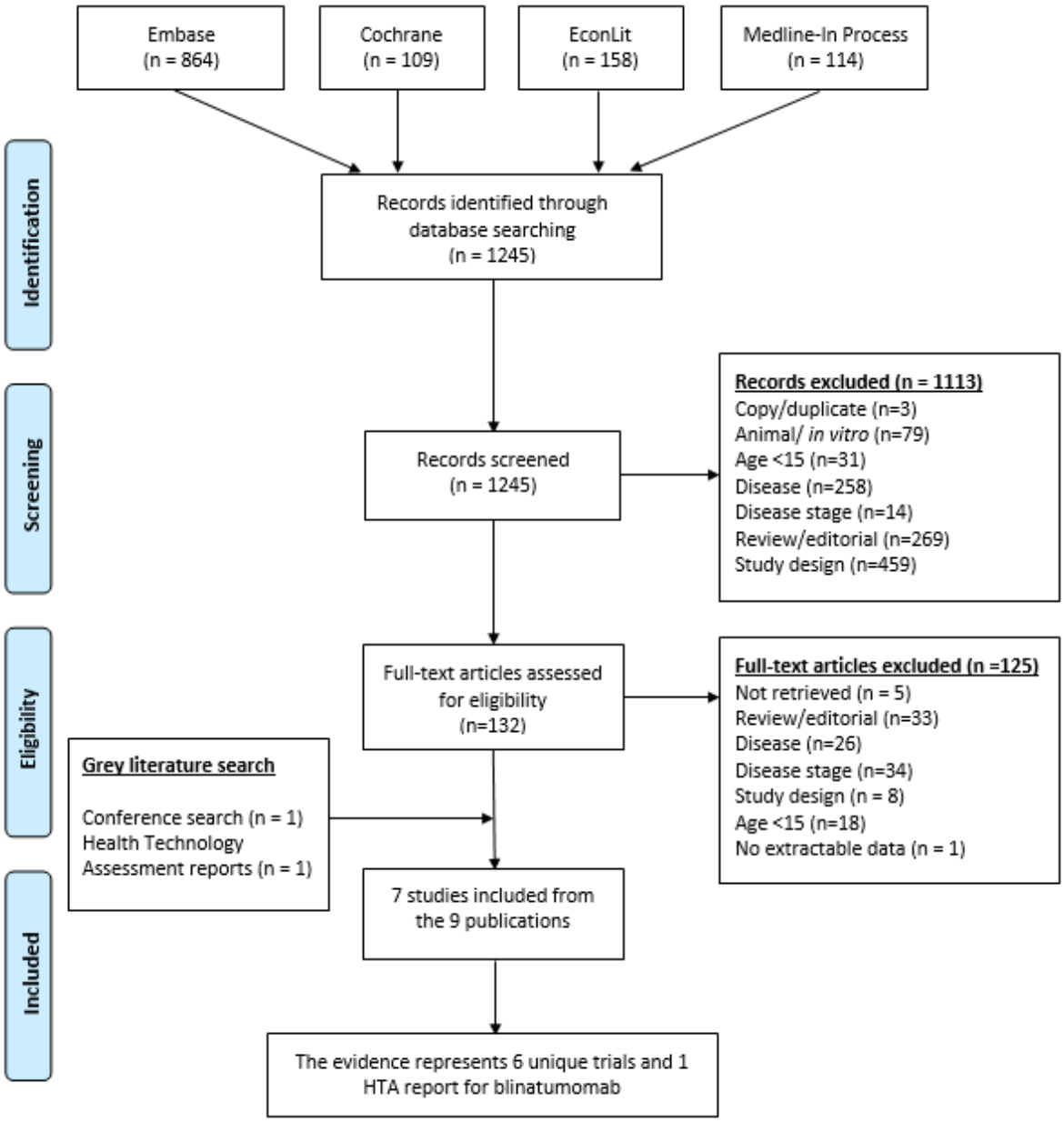
The full-text articles were obtained for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by one reviewer against each eligibility criterion. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

5.4.3.3. PRISMA flow diagram from HRQL SLR

As shown by the PRISMA diagram in Figure 51, 1,245 potentially relevant papers or abstracts were identified for the utility review. A de-duplication step was performed to remove studies that overlapped across the databases, and thus, three studies were identified as duplicates and excluded. The remaining studies were screened based on the information reported in their titles and/or abstracts. Of these, 1,113 were excluded at the primary screening stage as they were not of relevance to the research question. These papers were excluded for reasons such as being non-systematic reviews/editorials (n=269), having incorrect study designs (n=459), investigating diseases other than ALL (n=258) or being animal/*in vitro* studies (n=79).

A total of 132 articles were assessed in full for further evaluation. Of these, 120 were excluded, and five were unobtainable (see Appendix 8.3 for details of these studies), leaving seven papers to be included in the review. Papers were excluded for reasons such as being reviews/editorials (n=33), patients being <15 years old (n=18), having incorrect study designs (n=8) and investigating diseases other than ALL (n=26) and patients with newly diagnosed ALL (n=34). Additionally, one record each was included from conference and websites searches, respectively. Therefore, nine citations were included. Due to multiple publications for a single study, seven extractions were done from nine publications.

Figure 50: PRISMA diagram for utility review



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5.4.3.4. Overview of included studies

Seven studies were included in the utility/HRQL review (Table 55). This included six journal articles[18, 111, 130, 154-156] and one HTA.[137]

There were four studies evaluating adults with R/R ALL: three unique publications[18, 111, 130] and one HTA.[137] One study did not include assessment of an intervention.[18] This study was conducted to develop, validate and value the health states in members of the general UK population. Two of these four publications assessing adults with R/R ALL reported both the response rates and cohort size.[18, 111] Three studies were conducted in the UK[18, 130, 137], and one study did not report the country setting.[111] However, the latter presented the patient-reported outcomes (PRO) results from the INO-VATE 1022 trial.

Of the seven included studies, three recruited patients aged >15 years (not specifically an adult population); ALL was diagnosed in these patients in childhood, and they are thus not relevant to the decision problem considered within this submission, but were extracted for completeness within the SLR

Table 55: Key characteristics of utility/health-related quality of life studies

Study name	Intervention(s)/ comparator(s)	Country/ Setting	Type of study	Key assumptions	Cohort size	Response rates
Aristides 2015	None[a]	UK	Population-based survey: utility study	• Adverse events that patients may experience during treatment were not included in the health state descriptions to keep the health state utility values independent of the treatment received • Terminology regarding cancer or leukaemia was not included in the health state descriptions based on the conclusions of a study that found that including a cancer label in health state descriptions negatively affects health state values • A few considerations based on the pilot study[b]	123 participants were recruited and included in the final analysis	All the participants responded. Thus, the response rate was 100%
Iannazzo 2015[c]	• Ponatinib[d] • BSC	UK	Economic modelling study	In the absence of utilities evaluated for Ph+ ALL, health state utilities were assumed to be the same as in BP-CML	NR	NR
Kantarjian 2016	• Inotuzumab • SoC	NR	HRQL	NR	• Inotuzumab: 141 • SoC:138	• PROs completion rates • Inotuzumab: 85% • SoC: 64%
Blinatumomab SMC No. 1145/16	• Blinatumomab • SoC: FLAG-IDA	Scotland (UK)	Cost-utility study	Patients who were alive beyond 60 months were assumed to be cured	NR	NR

Key: ALL, acute lymphoblastic leukaemia; BP-CML, blast-phase chronic myeloid leukaemia; BSC, best supportive care; CT, chemotherapy; HRQL, health-related quality of life; InO, inotuzumab ozogamicin; NR, not reported; Ph+, Philadelphia chromosome positive; PRO, patient-reported outcome; RT, radiotherapy; SoC, standard of care; SCT, stem cell transplantation.
Notes: [a] Study was conducted in general population of UK (untreated); [b] *1.* The health states underwent reduce the length and make differences between the states clearer. *2.* A 'prior to treatment' statement was designed to introduce the participants to what it would be like to have B-precursor ALL. This description was the same for each post-treatment health state. *3.* Small simplifications to questionnaires were made, and participants would be able to indicate their preference for a health state by circling it;
[c] Poster also available; [d] Followed by alloHSCT in patients with MCyR

The outcomes sought in this review were utility and HRQL data, as presented in Table 56. Of the four publications that evaluated adult patients with R/R ALL, three reported health states for which utility values were estimated.[18, 130, 137] Time trade-off methodology was used to value the health states in two publications.[18, 137] The remaining study used EORTC QLQ-C30, EQ-5D and EQ-5D VAS to assess HRQL; only this study reported data on HRQL derived from patient-reported outcomes.[111]

As previously presented in Section 4.7, data from the INO-VATE 1022 study showed that patients receiving inotuzumab reported numerically better HRQL[111], functioning and symptom scores at each cycle versus SoC. The least mean squares score of physical and role functioning was significantly different for inotuzumab compared to SoC (7.6 vs 11.5; p<0.02). Furthermore, mean treatment differences were in favour of inotuzumab in EQ-VAS, global health status/QoL, social functioning, dyspnoea, appetite loss and fatigue and exceeded or approached a score of 5 (generally considered the minimally important difference [MID] to be clinically meaningful), although without statistical significance. Other dimensions directionally favoured inotuzumab, except for the dimension of emotional functioning, constipation, and pain, but none approached the MID.

Aristides et al. reported a study using time trade off methodology in a sample of the UK population to determine develop, validate and value the health states for patients with R/R B-cell, the mean EQ-5D score for the participants was (mean utility [SEM]), 0.91 (SD: 0.17).[18] Complete remission was the most preferred health state (mean utility [SEM], 0.86 [0.01]), followed by complete remission with partial haematological recovery (with minimal risk of bleeding or developing infection) (0.75 [0.02]); aplastic bone marrow (0.59 [0.02]); partial remission (0.50 [0.03]); and progressive disease (0.30 [0.04]). Within the HE model for ponatinib reported by Iannazzo et al., utility scores for patients in health states depicting response and no response were reported to be 0.56 and 0.29, respectively.[130]

In the SMC advice for blinatumomab, the utility values applied to both the considered health states were 0.84 for *remission* and 0.35 for *progressive death*. The utility value increased to 0.86 for patients who were alive beyond 60 months, as these patients were assumed to be cured (with general population mortality).[137]

Quality assessment of the included studies was carried out using the Papaioannou et al. checklist[157], and the results are presented in Appendix 8.4.

Table 56: Utility/health-related quality of life outcomes

Study name	Intervention/ comparator	Description of health states and source of definitions	Method of elicitation and valuation	HRQL data	Utility data	Adverse event utilities/ disutilities
Aristides 2015	None	• CR • CRh • aBM • PR • PD	TTO	NR	**Health state** / **Mean (SEM)** / **Increment (SEM)** CR: 0.86 (0.01) / 0.56 (0.042) CRh: 0.75 (0.02) / 0.45 (0.038) aBM: 0.59 (0.02) / 0.29 (0.034) PR: 0.50 (0.03) / 0.20 (0.032) PD: 0.30 (0.04) / --	NR
Iannazzo 2015	• Ponatinib[a] • BSC	• Ph+ ALL-response • Ph+ ALL-no response • Post-alloHSCT • Adverse event	NR	NR	• Ph+ ALL-response: 0.56 • Ph+ ALL-no response: 0.29 • Post-alloHSCT • Cycle 1: 0.55 • Cycle 2: 0.63 • Cycle 3: 0.71	Adverse event: 0.52
Kantarjian 2016	• InO • SoC	NR	• EORTC QLQ-C30 • EQ-5D • EQ-5D VAS	**Physical and role functioning** • InO: 7.6; p<0.02 • SoC: 11.5	NR	NR
Blinatumomab SMC No. 1145/16	• Blinatumomab • SoC: FLAG-IDA	• Remission (CR; CRh; CRsg) • PD (PD; aplastic bone marrow or PR)	TTO	NR	• Remission health state: 0.84 • PD health state: 0.35 • For patients who were alive beyond 60 months, the utility values increased to 0.86 as these patients were assumed to be cured	NR

Study name	Intervention/ comparator	Description of health states and source of definitions	Method of elicitation and valuation	HRQL data	Utility data	Adverse event utilities/ disutilities
		• Death				

Key: aBM, aplastic bone marrow; ALL, acute lymphocytic leukaemia; alloHSCT, allogenic haematopoietic stem cell transplantation; BSC, best supportive care; CR, complete remission; CRh, complete remission with partial haematological recovery; CRsg, complete remission by study group; CT, chemotherapy; FLAG-IDA, combination of fludarabine, cytarabine, idarubicin, and granulocyte-colony stimulating factor (G-CSF); NR, not reported; PD, progressive disease; Ph+, Philadelphia chromosome positive; PR, partial remission; RT, radiotherapy; SEM. Standard error of the mean. SoC, standard of care; SCT, stem cell transplantation; SF-36, short form 36; TTO, time trade-off.
Notes: [a] Followed by alloHSCT in patients with major cytogenic response;

5.4.4. Adverse reactions

Section 4.12 reports the incidence of Grade 3 or higher AEs within the INO-VATE 1022 study. All Grade 3 or higher AEs that occurred in at least 5% of the patients treated within the INO-VATE 1022 study are included in the model as this is in line with previous oncology models[158] and was considered an acceptable criterion by UK clinicians at a recent advisory board.[48] GvHD, as a potential but serious implication of HSCT, was also included within the model; however, INO-VATE 1022 only captured deaths due to GvHD. Therefore, to ensure that the incidence was not underestimated, rates were taken from Kiehl et al. 2004, assuming that the GvHD rates were not treatment specific as they are related to HSCT. This seemed a reasonable assumption given that GvHD is a result of the HSCT procedure itself and the quality of the patient-donor match as opposed to a direct side-effect of treatment.[159] The Kiehl et al. study was deemed an appropriate source as it was a large study (n=264), assessing HSCT of adult patients in a specific ALL population. All AEs and incidence rates are reported in Table 57. Because HRQL was captured using the EQ-5D instrument within the INO-VATE 1022 study, the utility values obtained for each level of remission already accounts for decrements due to the occurrence of AEs. No additional decrements were therefore applied to the inotuzumab or SoC arms in the model in order to avoid double counting, except for the occurrence of VOD. This is in line with previous methodology accepted by NICE.[158] However, as some patients in the inotuzumab arm experienced VOD while on treatment (a result of prior HSCT), and these disutilities would already be reflected in the EQ-5D, the inclusion of disutility for VOD is double-counting which would produce a conservative estimate of inotuzumab's QALYs.

VOD is a serious complication associated with HSCT. Within the INO-VATE 1022 study, there was a higher incidence of VOD in the inotuzumab arm than would be expected in UK clinical practice. However, it is important to note that this incidence is heavily driven by Japanese patients within the clinical trial. Japanese treatment is very different to that elsewhere, particularly with regard to the typical conditioning regimens administered, which in Japan is ThioTEPA which is associated with an increase in the incidence of VOD. ThioTEPA is not typically administered within the UK due to the associated risks of VOD and other AEs. This is shown within the data where post HSCT, [redacted] of Japanese patients in the inotuzumab arm and [redacted]

[redacted] of Japanese patients in the SoC arm experienced VOD, and a larger proportion of inotuzumab patients were treated in a Japanese setting than the SoC arm. In the non-Japanese population only [redacted] of patients in the inotuzumab arm had VOD, compared to [redacted] in the SoC arm. Although the patient numbers for Japanese patients in the post-HSCT health state are very small, these data show how the difference in transplantation in Japan may potentially be increasing the overall incidence rates of VOD. Table 57 shows the incidence rates for the total population and the non-Japanese patient population. In the base case, the incidence of VOD was taken from non-Japanese patients only; however, the incidence of the entire population was explored in scenario analysis.

No HRQL data were found in the literature in relation to VOD; however, in the defibrotide manufacturer submission to the SMC, the assumption was made that quality of life with severe VOD was approximately the same as acute liver failure prior to a transplant.[160] The utility associated with liver failure prior to transplant was 0.208. The average duration of VOD in the INO-VATE 1022 trial was 26.8 days; therefore, the utility value of 0.208 was applied to patients with VOD for 1 cycle (28 days) after HSCT, to reflect the poor quality of life experienced by patients at the occurrence of the event. However, due to the availability of defibrotide to treat VOD, which was not available to all trial patients during the trial, quality of life and risk of death related to VOD is expected to be lower in UK practice. As such, a disutility of 0.208 is likely to be an over-estimate of the impact to HRQL in practice. In order to take a conservative approach, however, as VOD impacts the inotuzumab arm more than the SoC arm, the high disutility is applied, however the higher cost of defibrotide is also applied (but without the benefit). This will produce a more conservative ICER for inotuzumab.

The disutility value associated with GvHD was captured in the HRQL data for post-HSCT utilities from Kurosawa et al. (2016) (see Section 5.4.5)[161]

Table 57: Adverse event rates used in the model

Adverse event	InO	SoC	Source
Adverse events on treatment			
Neutropenia	[redacted]	[redacted]	INO-VATE 1022[3]
Thrombocytopenia	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	
Febrile neutropenia	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	
Lymphopenia	[redacted]	[redacted]	
White blood cells decreased	[redacted]	[redacted]	
Veno-occlusive liver disease	[redacted]	[redacted]	
Adverse events post-HSCT			
Veno-occlusive liver disease	[redacted]	[redacted]	INO-VATE 1022 (safety population)[3]
Veno-occlusive liver disease (non-Japanese patients)	[redacted]	[redacted]	INO-VATE (safety population) 1022[3]
Graft versus host disease	11.34%	11.34%	Kiehl et al. (2004)[159]

Key: InO, inotuzumab ozogamicin; HSCT, haematopoietic stem cell transplant; SoC, standard of care.

5.4.5. Health-related quality-of-life data used in cost-effectiveness analysis

For the progression-free patients, treatment-specific utilities obtained from the EQ-5D data collected within the INO-VATE 1022 trial were used to inform the remission health states (reported in Section 5.4.1). The model uses treatment-specific utilities in the base case, which are applied at baseline in Cycle 0, then from Cycle 1 based on the level of remission. As the baseline utility for inotuzumab is slightly higher at baseline than the SoC (0.69 and 0.67, respectively), scenario analysis was conducted that used pooled utilities applied to each health state to ensure any potential bias was explored. However, using the utilities from the start of treatment render a conservative estimate of comparative HRQL, as the 5 to 6 day inpatient admission for administration SoC versus the anticipated outpatient administration for

inotuzumab (should these patients not be hospitalised for other reasons), is likely to reduce the HRQL of the SoC arm.

The utility estimates from the end of treatment from the INO-VATE 1022 trial (reported in Section 5.4.1) are used to inform the '*no CR/CRi* & no HSCT*'* and '*CR/CRi & no HSCT*' health states, with values of [redacted] and [redacted] (for inotuzumab and SoC) and [redacted] for the health states, respectively. These utilities are tested in probabilistic sensitivity analysis (outlined in Section 5.7) to test the parameter uncertainty associated with the utility values. This utility is applied from Cycle 1 onwards until progression. The end of treatment estimate reflects the quality of life of the patient after the last treatment cycle. The on treatment pooled utilities are also explored through scenario analysis.

The baseline utility and end of treatment utility is only applied to patients if they did not undergo an HSCT, progress or die.

The utilities from the trial for the health state '*no CR/CRi* & no HSCT*'* for inotuzumab and SoC of [redacted] and [redacted], respectively, have external validity as they are similar to those found within the literature. Aristides et al. (2015)[18] report that their study assigned utility values to health states experienced by R/R B-cell ALL patients using time trade-off (TTO). This study reported a partial remission utility of 0.50 and 0.75 for the complete remission with partial haematological recovery (the trial results reported a utility of [redacted]); these values are summarised in Table 56.

No HRQL data for patients with ALL who had undergone a HSCT were identified from the SLR; therefore, data reported by Kurosawa et al. were used in the model. Kurosawa carried out a decision analysis comparing allogeneic haematopoietic cell transplant (allo-HCT) versus chemotherapy in acute myeloid leukaemia (AML), which was used to inform these estimates. An assumption was made that patients with AML post-allo-HCT experience a similar utility of ALL patients post-HSCT, which was validated through consulted clinical expert opinion.[162] Table 58 presents the overall utilities used for post-HSCT patients, which are: for less than 1 year post-HSCT (0.59), 1–2 years post-HSCT (0.75), 3 to 5 years post-HSCT (0.74) and 5 years post-HSCT (0.76), until death. These are applied to patients in the model for the corresponding time after they receive a HSCT. Expert clinicians were consulted, and utility values reported by Kurosawa et al. were deemed appropriate (in the absence

of relevant utilities from the study) due to being the most recent and relevant publication available.[162]

It is worth noting that 3 years post-HSCT is when patients are deemed 'cured' (see Section 5.3) and patients follow general population mortality estimates from this point onwards. However, patients' HRQL is assumed to be the same as the Kurosawa et al. paper (with a value of 0.76), not equivalent to the utility of the general population which has been assumed in previous models with a cure point.[150, 163] The utility applied within the model post 3 years of HSCT is substantially lower than the anticipated general population utility. A value of 0.74 from Kurosawa et al. is used as opposed to 0.87 (normal population utility estimated using the algorithm presented by Ara and Brazier[164] at age 49, using the average age of 46 at the start of the model, and the baseline gender split). Therefore, the model approach may be considered to be a conservative approach in comparison to similar model structures in different disease areas as more patients reach HSCT with inotuzumab (and benefit from the utility post-HSCT) than in SoC..[137, 150] Furthermore, as outlined in Section 3.2, HRQL can improve beyond baseline over time after HRQL.

The utility used for progression in the model is 0.3, taken from Aristides et al. (2015).[18] For post-HSCT progressed patients, scenario analysis explored the cost-effectiveness when the same utility values are used post-HSCT regardless of progression status. Within this scenario, only utility values derived from Kurosawa et al. (2016), described above, are applied.[161] This scenario assumes that progression status post-HSCT is not a relevant consideration in a patient's HRQL. All utility values included in the model are summarised in Table 58.

Further to this, scenario analysis was also conducted that explored the cost-effectiveness of inotuzumab versus SoC when alternative utility values were sourced from the literature. Within this scenario, utility values were taken from the SMC appraisal of blinatumomab (see Section 5.4.3) where a utility of 0.84 is applied for remission health states, 0.35 is applied for progression and after the cure point at 60 months (see Section 5.3), a utility of 0.86 is applied.

Table 58: Summary of utility values for cost-effectiveness analysis

State		Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Baseline		InO: 0.69 (0.02) SoC: 0.67 (0.03) Pooled: 0.69 (0.02)	0.65–0.74 0.62–0.73	Section 5.4.1, page 198	Assumed base line utilities collected in INO-VATE 1022 represent the base line patient population before treatment.
No CR/CRi & no HSCT		[redacted]	[redacted]	Section 5.4.1, page 198	Assumed the end of treatment utility from INO-VATE 1022 represents HRQL in this health state.
CR/CRi & no HSCT		[redacted]	[redacted]	Section 5.4.1, page 198	Assumed the end of treatment utility from INO-VATE 1022 represents HRQL in this health state.
Post-HSCT	<1 year post	0.59 (0.10)	0.40–0.78	Section 5.4.5, page 211	Assumed that AML utilities after HSCT from Kurosawa et al. (2016) can be applied to R/R ALL patients. These include the disutility for GvHD.[161]
	1–2 years' post	0.75 (0.03)	0.69–0.82		
	3–5 years' post	0.74 (0.02)	0.70–0.78		
	>5 years post	0.76 (0.03)	0.71–0.81		
Progression		0.30 (0.04)	0.22–0.38	Section 5.4.5, page 211	Taken from the study by Aristides et al. (2015).[18]
VOD after HSCT applied for one cycle		0.208	NA	Section 5.4.4, page 209	Assumed to be approximately the same as acute liver failure pre-transplant. (SMC).[160] This is a conservative approach, as reasons described above.

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Key: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CR, complete remission; CRi, complete response with incomplete count recovery; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; InO, inotuzumab ozogamicin; NA, not applicable; SoC, standard of care; VOD, veno-occlusive disease.				

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1. Resource identification, measurement and valuation studies

5.5.1.1. Identification of studies

A SLR was conducted with the objective of identifying the healthcare resource utilisation and the direct and indirect costs related to R/R ALL. The search was conducted between 5 and 6 September 2016.

The full search strategies used in the electronic searches are provided in full in Appendix 9.1. The cost and resource use SLR searched the same databases, conference proceedings and HTA websites as the cost-effectiveness SLR reported in Section 5.1.1. Search strategies were designed using filters validated by SIGN, and all relevant studies in English were included (no relevant non-English language articles were identified at the screening stage).

The searches were limited to those published since 2000 to focus on the most recent cost data. This restriction was applied as considerable changes were observed in the costs and resource use of treatments, advances in technology (drug therapy, diagnostics, etc.), quality/SoC, overall standards of living and inflation over a period of 16 years (2000–2016). The search was also restricted to studies conducted in the UK; therefore, costs were specific to the NHS.

5.5.1.2. Study selection criteria

The detailed inclusion/exclusion criteria for cost and resource use studies are presented in Table 59. Studies that assessed mixed disease populations (e.g. R/R ALL and treatment-naïve ALL or R/R ALL and other malignancy/ies) were included only if separate data were reported for R/R ALL. Similarly, studies that assessed

both paediatric and adult patients were included only if subgroup data were available for patients >15 years of age. Letters and citations without an abstract were not included. Cost and resource use data reported for non-treated patients were also included.

Table 59: Inclusion and exclusion criteria for cost and resource use studies

Criteria	Inclusion	Exclusion
Population	Patients aged at least 15 years[a] Patients diagnosed with R/R ALL	Paediatric patients Patients with newly diagnosed ALL
Intervention/ comparator	No restriction	Studies were not excluded based on intervention or comparator therapy
Outcomes	Cost data (direct or indirect, unit or total) Resource use data Cost of managing treatment-related adverse events	No restriction
Study type	Cost and/or resource use studies, i.e. economic/clinical studies reporting cost and/or resource use data for population of interest Systematic review[b]	Non-systematic reviews[a], letters and comment articles Studies not reporting cost and/or resource use data
Language	Studies published in English Studies published in non-English languages were included and flagged[c]	Studies were not excluded based on publication language
Publication timeframe	Studies published in or after 2000 (last 16 years)	Published before 2000
Country	UK	

Key: ALL, acute lymphoblastic leukaemia; R/R, relapsed/refractory.
Notes: [a] Systematic reviews were included and flagged for bibliography searches; [b] Studies published in languages other than English were to be explored only if sufficient evidence was not identified from English language studies; [c] Studies published in languages other than English were to be explored only if sufficient evidence was not identified from English language studies.

Each reference (title and abstract) was independently reviewed by one reviewer by applying the basic selection criterion specified in Table 59. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

The full-text articles were obtained for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by one

reviewer against each eligibility criterion. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

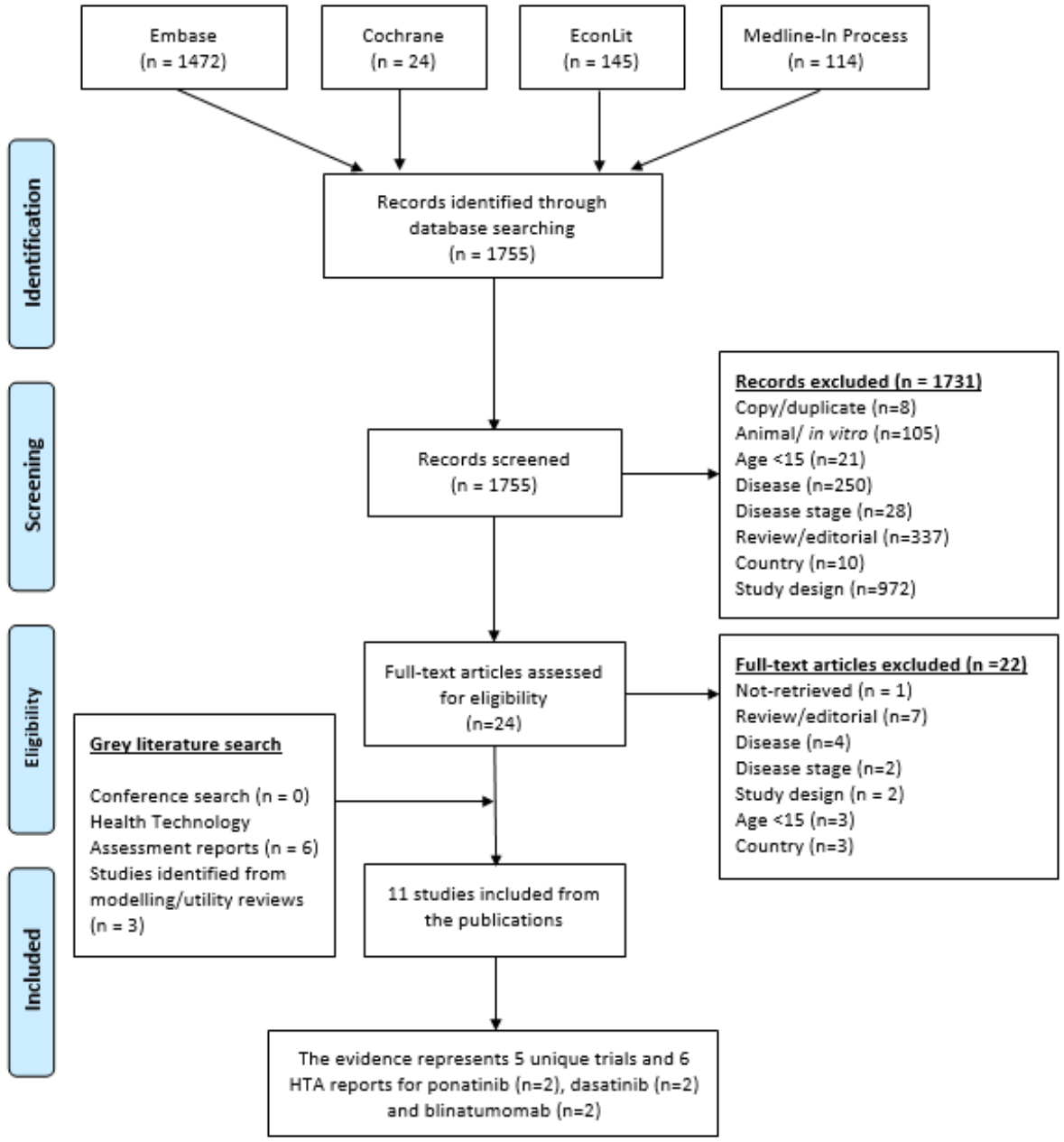
5.5.1.3. PRISMA flow diagram from the cost and resource use SLR

A total of 1,755 potentially relevant papers or abstracts were identified for the cost and resource use review. A de-duplication step was performed to remove studies that overlapped across the databases, and thus, eight studies were identified as duplicates and excluded. The remaining studies were screened based on the information reported in their titles and/or abstracts. Of these, 1,731 were excluded at the primary screening stage as they were not of relevance to the research question. These papers were excluded for reasons such as being reviews/editorials (n=337), having incorrect study designs (n=972), investigating diseases other than ALL (n=250) or being animal/*in vitro* studies (n=105).

Twenty-four articles were assessed in full for further evaluation. Of these, 21 were excluded, and one was unavailable for inclusion in this draft of the SLR, leaving two papers to be included in the review. Papers were excluded for reasons such as being reviews/editorials (n=7), patients being <15 years old (n=3), having incorrect study designs (n=2), investigating diseases other than ALL (n=4) or country other than UK (n=3). Additionally, three records and six HTAs were included from economic modelling/utility reviews and websites searches, respectively. Therefore, 11 citations were included for this review.

The details for flow of studies are presented in Figure 52 as a PRISMA flow diagram.

Figure 51: PRISMA diagram for cost and resource studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5.5.1.4. Overview of included studies

Eleven publications were identified for the cost and resource use review as presented in Table 60. This included one abstract publication[130] and six HTAs (two HTAs each for ponatinib[132, 134] and blinatumomab[135, 137] and dasatinib[138, 139]). Four NIHR briefing documents were also identified.[165-168] The cost year used was not reported in eight studies.[132, 134, 135, 139, 165-168] One study used a cost year of 2014[130],

and one study used costs from 2016.[137] In another study, costs were inflated to 2006 (in cost-utility analysis) and 2008 (in budget impact analysis).[138] The costs were measured in pounds (£) across all the studies. A discount rate of 3.5% was applied in four studies, which is in accordance with the NICE reference case.[130, 132, 135, 137]

Table 60: Key characteristics of cost and resource use data

Study name	Intervention(s)/ comparator(s)	Country	Type of study	Cost year/ currency	Discount rate
Abstract					
Iannazzo et al., 2015[a]	• Ponatinib[b] • BSC	UK	CE	• 2014 • Pounds (£)	3.5% per annum[c]
National Institute for Health Research reports					
Blinatumomab NIHR HSRIC ID: 3067	• Blinatumomab	EU (including UK), USA, Canada, Russia and Australia	Cost only	• NR • Pounds (£)	NR
Blinatumomab NIHR HSRIC ID: 9915	• Blinatumomab	UK	Cost only	• NR • Pounds (£)	NR
Vincristine liposomal (Marqibo®) NIHR HSRIC ID: 2401	• Vincristine liposomal (Marqibo)	UK	Cost only	• NR • Pounds (£)	NR
Inotuzumab ozogamicin NIHR HSRIC ID: 7550	• Inotuzumab	EU (including UK), USA, Canada and other countries	Cost only	• NR • Pounds (£)	NR
HTA – SMC					
Ponatinib SMC No. 1032/15	• Two economic analysis: • Ponatinib vs SCT • Ponatinib vs BSC	UK	CU and BIA	• NR • Pounds (£)	NR
Blinatumomab SMC No. 1145/16	• Blinatumomab • SoC: FLAG-IDA	Scotland (UK)	CU	• 2016 • Pound (£)	3.5% for outcomes
Dasatinib (Sprycel®) SMC No. 371/07	• Dasatinib • Imatinib • BMT	Scotland (UK)	Economic analysis	• NR • NR	NR
HTA – AWMSG					
Blinatumomab (Blincyto)	• Blinatumomab • SoC: FLAG-IDA	All Wales (UK)	CU and BIA	• NR • Pound (£)	3.5% for cost as well as outcomes
Dasatinib (Sprycel) Advice no. 1407	• Dasatinib • Imatinib • SCT	All Wales (UK)	CU and BIA	• Costs inflated to 2006 (CU) and 2008 (BIA) • Pound (£)	NR

Study name	Intervention(s)/ comparator(s)	Country	Type of study	Cost year/ currency	Discount rate
Ponatinib (Iclusig) Ref number: 1163	• Ponatinib • SCT • BSC%	Wales	CE and BIA	• NR • Pound (£)	3.5% for cost as well as outcomes

Key: AWMSG, All Wales Medicines Strategy Group; BIA, budget impact analysis; BMT, bone marrow transplant; BSC, best supportive care; CE, cost effectiveness; CU, cost utility; FLAG-IDA, combination of fludarabine, cytarabine, idarubicin and granulocyte-colony stimulating factor (G-CSF); HSRIC, Horizon Scanning and Research Intelligence Centre; NIHR, National Institute for Health Research; NR, not reported; SCT, stem cell transplantation; SoC, standard of care; SMC, Scottish Medicines Consortium.
Notes: [a] Poster associated with abstract was also identified; [b] followed by alloHSCT in patients who achieve major cytogenic response; [c] discount rate was applied for the economic model; [d] Comparator treatment sequences for the Ph+ ALL indication were based on whether patients were suitable or unsuitable for SCT.
For patients who were suitable for SCT, the relevant treatment sequences were:
• Ponatinib, followed by SCT (Ponatinib, SCT) in those patients who respond to it; BSC is applied after ponatinib discontinuation
• Entire modelled population starts on SCT (SCT).
For those patients not suitable for SCT, the relevant treatment sequences were:
• Ponatinib treatment, followed by BSC in case of discontinuation
• Patients are only given palliative chemotherapy (BSC).

Quality checks of studies providing data for cost and resource use were undertaken using the NICE critical appraisal for RCTs[169] and the Downs and Black checklist for non-RCTs.[108] This SLR did not identify a study that focused only on costs and resource in R/R B-cell ALL; the results reported are taken from relevant HTAs (n=10) and a single publication reporting a HE model.

Table 61: Cost and resource use data

Outcomes	Study name	Results
Input cost		
Resource use (input)	Blinatumomab (Blincyto®) SMC No. 1145/16	Patients were assumed to receive 1.64 cycles of blinatumomab (46 vials) and 2.18 cycles of FLAG-IDA
Cost of stem cell transplantation (input)	Iannazzo et al., 2015[a]	• **Per-cycle costs (monitoring and follow-up)** alloHSCT, Year 1: £14,303 alloHSCT, Year 2: £3,910 alloHSCT, Year 3+: £469 • **Per-event costs** alloHSCT, initial cost: £85,581
Treatment costs (input)	Iannazzo et al., 2015[a]	• **Per-cycle costs of ponatinib[b]:** £13,896 • **Per-cycle costs of BSC[c]:** £20,004
	NIHR HSRIC ID: 3067	Drug (FLAG ± anthracycline)-based regimen: cost per cycle (5 days) Idarubicin, fludarabine and cytarabine: £3023.80 (total cost for 1 cycle)
	NIHR HSRIC ID: 9915	Blinatumomab, a 35µg vial costs £2,017
	NIHR HSRIC ID: 2401	The cost of vincristine liposomal is not yet known. The cost of a 1ml vial (1mg/ml) of conventional vincristine sulphate is £10.92
	NIHR HSRIC ID: 7550	The cost of Inotuzumab ozogamicin is not yet known. The costs of other selected treatments for R/R ALL as used in the INO-VATE 1022 study are summarised as: • Cytarabine and fludarabine: £7,245.6 (total cost for four cycles) • High-dose cytarabine: £32,011.2 (total cost for one 12-dose cycle) • Cytarabine and mitoxantrone: £2,021.2 (total cost for four cycles)
	Ponatinib (Iclusig®) SMC No. 1032/15	**Cost per 28 days of ponatinib[b]:** £4,713 (45mg once daily, orally)
	Blinatumomab (Blincyto) SMC No. 1145/16	**Blinatumomab, continuous IV infusion: cost per cycle (£)** Cycle 1 (Day 1–7: 9mcg/day and Day 8–28: 28mcg/day): £ 48,408 Subsequent cycles (Day 1–28, 28mcg/day): £56,476 **FLAG-IDA:** £2,406 Cost of blinatumomab based on median exposure of 42 days in study MT103-114 is estimated to be £76,646
	Dasatinib (Sprycel®)	**Regimen cost for 52 weeks' treatment** Dasatinib, 70mg to 100mg twice daily: £31,627 to £63,254

Outcomes	Study name	Results
	SMC No. 371/07	Imatinib, 600mg daily: £29,194
	pCODR – ponatinib (Iclusig)	Ponatinib costs C$141.31 per 15mg or C$330.77 per 45mg tablet. At the recommended dose of 45mg per day, the daily cost of ponatinib is C$423.93 when using three 15mg tablets or C$330.77 when using one 45mg tablet. The cost per 28-day course is C$11,870.04 and C$9,261.56 when using three 15mg tablets and one 45mg tablet, respectively (from final recommendation)
	pCODR – blinatumomab (Blincyto®)	• Cost of blinatumomab: C$2,978.27 per vial (38.5mcg/vial) • At the recommended dose in first cycle (9mcg/day for the first 7 days and subsequently increased to 28mcg/day starting at Week 2 through to Week 4 of first cycle): C$1187.76–C$1443.32 per day • At the recommended dose in subsequent cycle: C$39,601.96–C$46,977.25 per 28-day cycle (in the initial recommendation: the cost per 28-day cycle of blinatumomab is C$33,257.25–40,424.93) • Cost of comparator, hyper-CVAD costs: C$126.29 per day and C$3536.19 per 28-day cycle Note: cost calculation for blinatumomab based on 48-hour infusion only
	Blinatumomab (Blincyto)	**Cost-effectiveness analysis:** • Blinatumomab, continuous IV infusion: Cycle 1 (Day 1–7: 9mcg/day and Day 8–28: 28mcg/day): £48,408 Subsequent cycles (Day 1–28, 28mcg/day): £56,476 • FLAG-IDA: £2,593 **Budget impact analysis:** For Years 1, 2, 3, 4 & 5: Cost of comparator displaced: £3,471
AE-related cost (input)	Iannazzo et al., 2015[a]	**Grade 3± AE costs: per event cost** • Abdominal pain: £573 • Anaemia: £1,830 • Lipase increased: £650 • Neutropenia: £105 • Thrombocytopenia: £2,275
Output cost		
Cost of stem cell transplantation (output)	Iannazzo et al., 2015[a]	• **Discounted costs for ponatinib**[e] alloHSCT: £49,375 • **Discounted costs for BSC** alloHSCT: --- • **Discounted costs for difference** alloHSCT: £49,375
Treatment costs	Iannazzo et al.,	• **Discounted costs for ponatinib**[e]

Outcomes	Study name	Results
(final)	2015[a]	TKIs: £9,187 Other drugs: £324 • **Discounted costs for BSC** TKIs: --- Other drugs: £240 **• Discounted costs for difference** TKIs: £9,187 Other drugs: £84
	Ponatinib (Iclusig) SMC No. 1032/15	**Base case results of incremental cost** • Ponatinib vs SCT: -£51,204 • Ponatinib vs hydroxyurea: £8,767 For the Ph+ ALL population, the company estimated there would be 15 patients eligible for treatment in Year 1 and four patients in Year 5 with an estimated uptake rate of 100% in all years and a 78% discontinuation rate. This resulted in an estimated three patients being treated in Year 1 and one patient in Year 5. The company estimated a gross budget impact of £279,000 in Year 1 and £69,000 in Year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £134,000 in Year 1 and £33,000 in Year 5
	Blinatumomab (Blincyto) SMC No. 1145/16	Incremental cost: £77,471
	pCODR – ponatinib (Iclusig)	Ponatinib is compared to hydroxyurea: • The extra cost of ponatinib is C$115,732 (ΔC). Costs considered in the analysis included drug costs, resource use costs and AE costs
	pCODR – Blinatumomab (Blincyto)	Extra cost; ΔC (C$), range/point: C$110,269
	AWMSG – blinatumomab (Blincyto)	**Base case analysis results**: **Drug cost:** • SoC: £3,471 **Other costs**[d] • Blinatumomab: £39,595 • SoC: £34,520 • Increment: £5,075
	AWMSG- Dasatinib (Sprycel)	**In cost-utility analysis:** Dasatinib 70mg twice daily compared to imatinib 400mg twice daily; incremental costs: £4,971

Outcomes	Study name	Results
	Advice no. 1407	**In budget impact analysis:** The budget impact of the use of dasatinib instead of imatinib in imatinib-resistant or intolerant patients has been estimated for each of the five years from 2008 to 2012. Assuming 100% uptake, the cost of using dasatinib instead of imatinib is estimated to save approximately £28,800 in 2008 and £29,300 in each of years 2009–2012 (i.e. dasatinib treatment is less expensive than imatinib treatment)
	Ponatinib (Iclusig) Ref number: 1163	**Data from budget impact model:** The company estimated annual costs of £30,300 for the two patients with Ph+ ALL per year eligible for ponatinib (based on a duration of treatment of approximately 3 months and the highest dose of ponatinib – 45mg per day) **Data from cost-effectiveness model:** Data were reported according to patients' eligibility for SCT: **Eligible for SCT: cost (£)** • Ponatinib, SCT: 78,097 • SCT: 129,192 **Unsuitable for SCT: cost (£)** • Ponatinib: 36,452 • BSC: 27,576
Administrative costs (final)	Blinatumomab (Blincyto)	**In budget impact analysis:** For Years 1,2,3, 4 and 5: Administration and monitoring: £12,660 Staffing: £313 Infrastructure: £176
AE-related cost (final)	Iannazzo et al., 2015	• **Discounted costs for ponatinib**[e] AEs: £456 • **Discounted costs for BSC** AEs: --- • **Discounted costs for difference** AEs: £456

Key: alloHSCT, allogenic haematopoietic stem cell transplantation; ALL, acute lymphocytic leukaemia; AEs, adverse events; AWMSG, All Wales Medicines Strategy Group; BSC, best supportive care; HSRIC, Horizon Scanning and Research Intelligence Centre; IV, intravenous; NIHR, National Institute for Health Research; Ph+, Philadelphia chromosome positive; SCT, stem cell transplantation; TKIs, tyrosine kinase inhibitors.
Note: [a] Poster associated with abstract was also identified; [b] Based on UK pack price; [c] Applied in first cycle only; [d] Inpatient and outpatient administration, day hospital costs, pump, CR and HSCT follow-up, HSCT administration and palliative care costs; [e] Ponatinib followed by alloHSCT in patients achieving a major cytogenetic response.

5.5.2. Intervention and comparators' costs and resource use

5.5.2.1. Drug acquisition costs

Drug acquisition costs are presented in Table 62. The cost presented for inotuzumab represents the proposed list price. The costs considered are in relation to the treatment and the SoC (consisting of FLAG/FLAG IDA, CM, HIDAC, and imatinib for Ph+ patients). FLAG IDA is the standard treatment for R/R B-cell ALL patients in the UK over FLAG alone, therefore the cost of idarubicin (IDA) was costed in the model base case (with efficacy of FLAG used as a proxy for FLAG-IDA). However, a scenario analysis was conducted that applies the cost of FLAG only as per the INO-VATE 1022 trial.

Table 62: Unit drug costs

Drug		Pack size	Cost	Cost per unit	Source
InO	1mg vial	1	[redacted]	[redacted]	Pfizer
Fludarabine	50mg vial	1	£23.43	£0.47/mg	eMit[170]
Cytarabine	1g/10ml vial	1	£5.75	£0.06/mg/ml	
	2g/20ml vial	1	£8.17	£0.08/mg/ml	
	100mg/1ml vial	5	£15.33	£0.03/mg/ml	
	100mg/5ml vial	5	£22.01	£0.22/mg/ml	
	500mg/5ml vial	5	£20.15	£0.04/mg/ml	
G-CSF	300µg/ml vial (1ml)	5	£263.52	£0.18/µg/ml	MIMS (Neupogen)[171]
	600µg/ml syringe (0.5ml)	5	£263.52	£0.18/µg/ml	
	960µg/ml syringe (0.5ml)	5	£420.29	£0.18/µg/ml	
	600µg/ml syringe (0.5ml)	5	£290.00	£0.19/µg/ml	MIMS (Nivestim)[171]
	960µg/ml syringe (0.5ml)	5	£465.00	£0.19/µg/ml	
	600µg/ml syringe (0.5ml)	5	£311.25	£0.21/µg/ml	MIMS (Ratiograstim)[171]
	600µg/ml syringe (0.8ml)	5	£496.44	£0.21/µg/ml	
	600µg/ml syringe (0.5ml)	5	£250.75	£0.17/µg/ml	MIMS (Zarzio)[171]

Drug		Pack size	Cost	Cost per unit	Source
	960µg/ml syringe (0.5ml)	5	£399.50	£0.17/µg/ml	
Mitoxantrone	20mg/10ml vial	1	£31.51	£15.76/mg/ml	eMit[170]
Idarubicin	5mg vial	1	£87.36	£17.47/mg	MIMS (Zavedos)[171]
	10mg	1	£174.72	£17.47/mg	
TKI (Imatinib)	100mg tablet	60	£973.32	£0.16/mg	MIMS (Glivec)[171]
	400mg tablet	30	£1,946.67	£0.16/mg	

Key: eMit, electronic market information tool; G-CSF, granulocyte-colony stimulating factor; MIMS, Monthly Index of Medical Specialities; TKI, tyrosine kinase inhibitor.

5.5.2.2. Dosing assumptions

For the treatment costs applied in the model, it was assumed that patients received only whole vials and there was no vial sharing. Using the weight and height data from the INO-VATE 1022 trial and the average actual dose taken per cycle, the average number of vials required per cycle was calculated using the 'method of moments' technique. The method of moments is a technique that allows the estimation of the average number of vials required per administration of a treatment where dosing is administered based on weight and height[172] (which is common in many ALL treatments). This method accounts for the distribution around a patient populations weight, as opposed to a point estimate, and works by fitting a lognormal distribution to body surface area (BSA) or weight data. The variation in BSA or weight was obtained from the individual patient data from the INO-VATE 1022 data. Using the lognormal distribution, the relative frequency of the dose and number of vials required is obtained. The method of moments then works out a weighted average of this to obtain an average number of vials necessary for administration, which is then applied within the economic model. The method accounts for drug wastage as it is based on the number of vials needed in total. The method of moments was used within the model wherever dosing was based on BSA or weight. The average number of vials required per cycle for each regimen is summarised in Table 63.

As idarubicin and imatinib were not included in the trial, the dosages for these were obtained from their SPC.[147, 173]

An alternative scenario is presented that calculates drug costs and dosing based upon the average BSA and weight from the INO-VATE 1022 trial data, including or excluding wastage (Section 0).

Table 63: Average number of vials required per cycle using method of moments based on mean actual dosing from the INO-VATE 1022 trial and SPC data[1, 3, 147]

Drug	Vial size	Mean actual dose by cycle	Average vials required using MoM	Number of patients per cycle	Total vials
InO	1mg	[redacted]	[redacted]	[redacted]	[redacted]
Fludarabine	50mg	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine (FLAG)	1g	[redacted]	[redacted]	[redacted]	[redacted]
G-CSF	300µg	[redacted]	[redacted]	[redacted]	[redacted]
Idarubicin	5mg	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine (CM)	100mg	[redacted]	[redacted]	[redacted]	[redacted]
Mitoxantrone	20mg	[redacted]	[redacted]	[redacted]	[redacted]
High dose cytarabine	2g	[redacted]	[redacted]	[redacted]	[redacted]
TKI (imatinib)	100mg	[redacted]	[redacted]	[redacted]	[redacted]

Drug	Vial size	Mean actual dose by cycle	Average vials required using MoM	Number of patients per cycle	Total vials
Key: CM, cytarabine plus mitoxantrone; FLAG, combination of fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF); MoM, method of moments; NA, not applicable; SPC, summary of product characteristics; TKI, tyrosine kinase inhibitor. **Notes:** [a] Based on the idarabicin SPC[173]; [b] Based on the ponatinib SPC and an average duration of treatment of 86 days.[174]					

The total treatment costs were calculated based on the cost per vial multiplied by the total number of vials received within the trial (or average dosing if the comparator is was not considered within the trial i.e. imatinib and IDA). The total cost per treatment was then applied as a lump sum in Cycle 0 for all patients. As treatment was only administered for a small number of cycles, and the exact data of dosing was available from the trial, treatment costs were calculated manually rather than fitting a time on treatment curve. The median number of treatment cycles was three cycles for inotuzumab and one for the SoC arm.

In line with UK clinician input, where they stated that inotuzumab would only be likely to be administered for a maximum of three cycles, scenario analysis explores the cost-effectiveness results when inotuzumab is applied for three cycles only. Using the INO-VATE 1022 trial data, this reduces the number of vials of inotuzumab administered from [redacted] vials to [redacted](based again on the time on treatment data). Within this scenario, it is assumed that efficacy remains the same, which is not unrealistic given [redacted] patients had responded to treatment by cycle three within the trial, which is in line with the anticipated time to response outlined by the UK clinicians.[48]

For the SoC arm, the total cost of treatment is based on the proportion of patients from the INO-VATE 1022 trial who took each combination therapy and was summed and applied in Cycle 0 also. Given the small number of treatment cycles, applying all the costs in Cycle 0 is unlikely to have any large impact on the discount rates applied within the model (discussion of discount rates in Section 5.2.2).

The proportion of patients who were Ph+ in the trial was used to calculate the total cost of imatinib in the SoC arm. This is applied on top of the other SoC treatments as it was assumed this would be administered alongside other chemotherapy for these

patients. A summary of the total drug acquisition costs per treatment arm is shown in Table 65.

5.5.2.3. Administration costs

A benefit of inotuzumab is that it is administered in an outpatient setting allowing patients to return home after infusion. This is contrary to other regimens licenced within ALL, including the standard of care comparator, which typically require inpatient stays every treatment cycle.

The administration cost of inotuzumab per cycle is based on the total number of administrations required per cycle multiplied by the cost of an outpatient visit obtained from NHS reference costs (See Table 64). The number of administrations required per cycle is three doses, as per the draft SPC (described in Section 2.3). These were then weighted using the proportion of patients that received each cycle and dose of treatment (obtained from the INO-VATE 1022 trial, see Table 63). Incorporating discontinuation rates, the average length of treatment was [redacted] cycles of treatment.

The SoC treatments (FLAG-IDA, CM, HIDAC) are administered in an inpatient setting. The length of inpatient stay (per cycle) was based on the SPC of each of the drugs. Imatinib (for use in combination with FLAG-IDA the Ph+ population) has not had an administration cost included as this is an oral medication and was therefore assumed that patients could self-administer. Based on the INO-VATE 1022 data, and incorporating discontinuation rates, the average length of inpatient stay on the SoC arm was [redacted] days. Table 64 summarises the administration costs applied to each treatment.

Table 64: Summary of administration costs

Treatment	Outpatient/ inpatient cost	Outpatient visits/ inpatient stays per cycle of treatment administered	Total cost per patient for the average course of treatment	Source

Treatment		Outpatient/ inpatient cost	Outpatient visits/ inpatient stays per cycle of treatment administered	Total cost per patient for the average course of treatment	Source
Inotuzumab		£304.30 per administration	3 administrations per cycle	**£2,582.80**	NHS reference costs[a175]
SoC	FLAG-IDA	£743.61 per inpatient day of administration	5 days inpatient	**£4,632.81** (weighted average based upon treatment use)	NHS reference costs[b175]
	CM		6 days inpatient		
	HIDAC		5 days inpatient		

Key: CM, cytarabine plus mitoxantrone; FLAG, fludarabine, cytarabine, granulocyte-colony stimulating factor; HIDAC, high dose cytarabine; NHS, National Health Service; SoC, standard of care.

[a]. NHS reference costs 15/16, Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, SB13Z. Outpatient

[b]. NHS reference costs 15/16, Acute Lymphoblastic Leukaemia with CC Score 0-1, SA24J, EL

5.5.2.4. Summary of drug acquisition and administration costs

Table 65 summarises the drug acquisition costs associated with inotuzumab and the comparators considered within the model. The table presents the total anticipated costs per patient. The SoC cost is estimated by taking a weighted average of the proportion of patients that received either FLAG-IDA, CM or HIDAC; the cost of imatinib is weighted by the proportion of patients who are Ph+ and added to the other SoC treatment costs.

Table 65: Drug acquisition costs (list price)

Drug		Total cost		
Inotuzumab		[redacted]		
Drug		**Cost**	**Proportion of patients**	**Total cost**
Standard of care	FLAG-IDA	[redacted]	[redacted]	[redacted]
	CM	[redacted]	[redacted]	
	HIDAC	[redacted]	[redacted]	
	TKI (Imatinib) Ph+ patients only	[redacted]	[redacted]	

Key: CM, cytarabine plus mitoxantrone; FLAG, fludarabine, cytarabine, granulocyte-colony stimulating factor; HIDAC, high dose cytarabine; IDA, idurabicin; InO, inotuzumab ozogamicin; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia chromosome positive.

5.5.3. Health-state unit costs and resource use

Disease monitoring was assumed to be captured in the outpatient/inpatient visit for administration and the adverse event costs. Therefore, no further health-state unit or resource use costs were applied.

5.5.4. Costs associated with HSCT

Costs associated with HSCT were taken from the study of NHS Blood and transplant (2014)[176] and uplifted to 2015/2016 prices using the Personal Social Services Research Unit (PSSRU)[177] inflated indices. This study breaks down the cost of HSCT and post-HSCT care using methodology from Agthoven et al. (2002).[178] The cost of an HSCT includes the cost of transplant unit personnel and transplantation which includes the cost of UK sourced cord blood donation.

Follow-up costs, shown in Table 66, are broken down into 6 months after HSCT, between 6–12 months after HSCT, and between 12–24 months after HSCT. The cost of an HSCT is applied to patients in the cycle they receive the HSCT and the follow-up costs are applied at the appropriate time point, post-HSCT. Within the model, it was assumed that the monthly cost was equal to the 28-cycle day length**.**

Table 66: Stem cell transplant and follow-up costs

Type of cost	Cost reported in NHS reference before inflation indices	Cost per cycle	Source
SCT cost	£58,903	£60,891.72	NHS blood and transplant (2014) uplifted from 2012/2013 to 2015/2016 prices using PSSRU inflation indices. (297.0/287.3)[176, 177]
Post-HSCT in first 6 months	£28,390	£4,891.42	
Post-HSCT from 6–12 months	£19,502	£3,360.07	
Post-HSCT from 12–24 months	£14,073	£1,212.35	

Key: NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HSCT, haematopoietic stem cell transplant.

Given the value of inotuzumab is that it allows patients to reach potentially curative therapy (HSCT), and the high costs associated with HSCT which is an independent treatment to what is being compared within this analysis (inotuzumab versus SoC), a scenario analysis is conducted which explores the cost-effectiveness of inotuzumab versus SoC where the costs of HSCT are removed.

5.5.5. Adverse reaction unit costs and resource use

All AEs of Grade ≥3 that also occurred in ≥5% of either treatment arm of the INO-VATE 1022 trial were included in the economic evaluation (see Section 5.4.3.1). The cost of treating the AEs in the model was calculated based on the frequency with which each AE occurred, multiplied by the unit cost of each AE. The frequency of the AEs was derived from the INO-VATE 1022 trial, and the literature was used to source the incidence of GvHD that had not been captured as a Grade 3 or 4 AE within the trial (see Section 5.4.4).

The costs of treating neutropenia, thrombocytopenia, leukopenia, febrile neutropenia, anaemia, lymphopenia and decreased white blood cells are based on NHS reference costs 2015/2016.[175]

The cost of treating VOD is based on the manufacturer submission for defibrotide to the SMC (2014).[160] Expert clinical opinion agrees that severe VOD is treated with defibrotide[48] in accordance with the guidelines of the British Committee for standards in Haematology.[129] From the cited SMC submission, the cost of defibrotide is £365 per 200mg vial and is administered at a dose of 6.25mg/kg every 6 hours for 21 days. Using the method of moments as outlined in Section 5.5.2.1, the total cost of defibrotide was £77,240.11. The published policy document from the NHS on the use of defibrotide in severe VOD following HSCT states that excess hospital stay due to severe VOD is 28.48 days.[179] The cost per inpatient stay in the defibrotide SMC submission was £1,879, based on 85% of patients requiring intensive care and 15% requiring high dependency care, which has been inflated to £1,921 using the PSSRU inflation indices.[177] Using this cost per hospital stay and the cost of defibrotide, the total cost for treatment of VOD is calculated to be £131,951.41. The SMC submission calculated that the total cost of defibrotide over a patient's lifetime was £92,836 (inflated to £94,913); however full information is unavailable to establish the differences between the two estimates. Therefore, in the model base

case, the average of the two calculations is used, and the lower estimate from the manufacturer submission is used as the lower bound, and the calculation based on INO-VATE 1022 average weight data is used as the upper bound.

However, defibrotide which was not available to all trial patients during the trial but both the trial outcomes and a disutility of 0.208 for VOD are used, both not reflective of the benefits to VOD. Further, some patients on inotuzumab incurred VOD while on treatment, so assigning these patients a disutility on top of their EQ-5D score is double-counting. Despite this, the full cost of defibrotide is included in the model, impacting the inotuzumab arm more than the SoC arm. Resultantly, it should be noted the approach to incorporating VOD in the economic model both reduces QALYs, but at a high treatment cost, thus producing a conservative ICER for inotuzumab. Table 67 summarises the costs used for VOD within the model.

Table 67: Costs of VOD treatment with defibrotide

Item	Value	Justification	Application	Source

Item	Value	Justification	Application	Source
Defibrotide (treatment only)	£77,240	Based on £365 per 200mg vial, 6.25mg/kg every 6 hours and average weight from INO-VATE 1022 trial.	Applied to the proportion of patients who have VOD on treatment.	SMC submission and INO-VATE 1022[3, 160]
Intensive care bed days	28.48			NHS policy[179]
Cost per inpatient stay	£1,921	Based on 85% intensive care and 15% high dependency care.		SMC submission inflated to 2015/16 prices[160, 177]
Defibrotide (upper bound)	£131,951	Based on cost of treatment only total cost of bed days.	Applied as an upper bound to the proportion of patients who have VOD after HSCT.	
Defibrotide (lower bound)	£94,913	Average cost over lifetime of patient.	Applied as a lower bound to the proportion of patients who have VOD after HSCT.	SMC submission inflated to 2015/16 prices[160, 177]
Defibrotide (base case)	£113,432	Based on the average of the upper and lower bound.	Applied in the base case to the proportion of patients who have VOD after HSCT.	

Key: HSCT, haematopoietic stem cell transplant; SMC, Scottish Medicines Consortium; VOD, veno-occlusive disease.

The cost of GvHD is based on a study from Espérou et al. (2004)[180] who reported that higher costs are associated with GvHD and multiple post-transplant episodes of bacterial, fungal, or viral infections. Within this study, these complications added an average of €20,000 to €30,000 to each transplant. To be conservative in the base case, it is assumed that GvHD is the highest of this range (€30,000); as more patients achieve HSCT with inotuzumab, this added a cost is incurred more in the inotuzumab arm, thus resulting in a more conservative ICER. This study was selected after conducting a targeted literature review to determine the costs associated with GvHD. From the search, Esperour et al. was considered the most appropriate source as it reported the additional costs associated with GvHD alone while other papers identified only SCT and GvHD costs combined. The €30,000 cost

of GvHD was converted to sterling using the 2004 exchange rate[181] and inflated to 2015/2016 prices using the inflation indices from PSSRU.[177]

Table 68 presents the AEs and the associated cost per episode that have been applied within the model.

Table 68: Cost of managing adverse events

Adverse event	Cost	Derived as	Source
Thrombocytopenia	£316.99	Weighted average day case cost: Thrombocytopenia A12G, SA12H, SA12J and SA12K	NHS reference costs[175]
Febrile neutropenia	£1,507.43	Weighted average Inpatient stay (Non-elective short stay and Non-elective long stay): Other Haematological or Splenic Disorders, weighted average Currency codes, SA08G, SA08H and SA08J.	
Neutropenia	£344.38	Weighted average day case cost: Other Haematological or Splenic Disorders SA08G, SA08H and SA09J	
Leukopenia	£344.38		
Anaemia	£344.38		
Lymphopenia	£344.38		
White blood cells decreased	£344.38		
VOD (on treatment)	£75,417.77	See Table 67	
VOD (post-HSCT)	£112,521.15	See Table 67	
GvHD (post-HSCT)	£26,888.92	Euros × conversion × inflation indices 30,000×1.47× (297.0/224.8)	Espérou et al. (2004) converted to £ using forex and inflated to 2015/2016 prices using PSSRU[177, 180]

Key: GvHD, graft versus host disease; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HSCT, haematopoietic stem cell transplant; VOD, veno-occlusive disease.

Using AE incidence rates from the INO-VATE 1022 trial, the total average cost of treating AEs while on treatment, per patient, is £576.41 in the inotuzumab arm and £1,239.23 in the SoC arm. As these costs are the average per patient, they are applied to all patients as a lump sum in Cycle 0. In addition, some patients may experience VOD prior to a HSCT if they have already undergone transplant

previously. The cost of treating VOD patients (pre-HSCT) with defibrotide is applied in Cycle 0.

The AEs costs post-HSCT are applied to patients who received an HSCT, applied to the patients in the first cycle post their HSCT. A summary of the costs associated with AEs on treatment and post-HSCT are shown in Table 69. It is noteworthy that the substantial increase in the proportion of patients receiving HSCT within the inotuzumab arm compared to SoC ([redacted] and [redacted] respectively as outlined in Section 5.3) increases the proportion of patients that can be exposed to AEs associated with HSCT.

Table 69: AE cost applied within the model

Treatment	AE cost on treatment	AEs post-HSCT	Total
Inotuzumab	£2,622.50	£11,088.67	£13,711.17
SoC	£1,239.23	£689.45	£1,928.68
Key: AE, adverse event; HSCT, haematopoietic stem cell transplant; SoC, standard of care.			

5.5.6. Miscellaneous unit costs and resource use

5.5.6.1. Subsequent induction treatments

Patients in the INO-VATE 1022 trial received subsequent induction treatments, such as blinatumomab, chemotherapy, TKIs and inotuzumab. The proportion of patients who receive each subsequent induction treatment in the model is taken directly from the INO-VATE 1022 trial. As these subsequent induction treatments (subsequent salvage therapy) may have impacted OS, including these treatments in the model minimises any bias. The entire list of subsequent treatment is presented in Table 15, however some treatments were not incorporated into the cost-effectiveness analysis as they are currently not administered in the UK setting and cannot be costed (*e.g.* CAR-T cell therapy) or alternatively were not considered for inclusion due to their relatively low cost (e.g. growth factors). Table 70 presents the proportion of patients who receive subsequent induction therapy in each arm.

Table 70: Proportion of patients who received each subsequent induction treatment

Subsequent induction therapy	InO	SoC
Blinatumomab	[redacted]	[redacted]
TKI	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]
Key: SoC, standard of care; TKI, tyrosine kinase inhibitor.		

Although available on Monthly Index of Medical Specialities (MIMS), the cost of blinatumomab is taken from the blinatumomab SMC submission[137] as this is an estimate of total treatment cost plus administration costs based on nine inpatient stays required for the first cycle and two required for the second cycle.[182] The cost of chemotherapy is assumed to be the weighted average of the SoC treatment costs including administration costs. For the TKIs, the cost of imatinib is applied based on an indication of 600mg per day. Information on the median duration of treatment for imatinib was limited and therefore the median duration was assumed to be 86 days, equal to that reported within the SPC for ponatinib, another TKI licenced for use in Ph+ ALL.[174] This is an oral treatment, and therefore, no administration costs have been included in the TKI cost. The cost also includes wastage. In the trial, ponatinib was used as the subsequent TKI treatment, however this is not a licenced therapy within the UK so imatinib has been used as an alternative. Given that there are a proportion of patients that may receive imatinib prior to subsequent induction therapy, there is the possibility that some patients in the SoC arm may be modelled to be treated with imatinib followed by imatinib, however this only impacts a patient's cost in the model and not their efficacy. It is noted that this would not be expected to happen in practice, however using an alternative TKI such as ponatinib has minimal effect on the ICER, so the assumption does not impact the model. The total cost of inotuzumab is based on the methods described in Section 5.5.2.1 plus administration costs. A breakdown of the subsequent induction treatment costs is presented in Table 71.

Table 71: Subsequent induction therapy costs used in the model

Subsequent induction treatment	Drug costs	Administration costs	Total cost	Source
Blinatumomab	£104,884.00	£8,179.70	£113,063.70	SMC blinatumomab[137]
TKIs (imatinib)	£8,759.88	n/a	£8,759.88	MIMS[171] Iclusig. EPAR. - EMEA/H/C/002695 - PSUSA/00010128/201412[174]
Chemotherapy	£4,198.08	£4,632.81	£8,830.90	See Section 5.5.2.1 and Section 5.5.2.3
Inotuzumab	[redacted]	£2,582.80	[redacted]	See Section 5.5.2.1 and Section 5.5.2.3
Key: MIMS, Monthly Index of Medical Specialties, SMC, Scottish Medicines Consortium, TKI, tyrosine kinase inhibitor.				

Subsequent induction treatment costs are multiplied by the proportion of patients who received subsequent induction therapy in each arm and then applied as a lump sum in Cycle 0 so each patient is afforded the average cost.

5.5.6.2. End of life costs

The cancer-specific end of life costs are based on the PSSRU (2016) for the cost of hospital and social care in the final year of life.[177] This cost of £11,616 is applied to patients upon death in the model. It is assumed within the model that this cost also incorporates the cost of treating a progressed patient

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1. Summary of base-case *de novo* analysis inputs

Appendix 10 summarises the base case inputs and variables. The scale of uncertainty around each parameter estimate was informed by data or assumptions as stated or as previously described in the previous sections. Parameters were explored through both probabilistic and one-way sensitivity analyses (OWSA).

Appendix 5.2 and 5.3 summarises the base case survival variables used to inform the parametric curves applied within the base case including input shape and scale

parameters, covariates, and the scale of uncertainty associated with these in the statistical analysis. Uncertainty around the survival parameters was explored through probabilistic sensitivity analyses and scenario analyses. Survival parameters were not used to inform OWSA as survival parameters of this kind are intrinsically linked to one another.[183]

An overview of the model schematic with key input data is presented in Figure 53.

Figure 52: Model overview diagram

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; INO, inotuzumab ozogamicin; OS, overall survival; QALY, quality-adjusted life year; SoC, standard of care.

5.6.2. Assumptions

The base case analysis that used data from the INO-VATE 1022 study was subject to several key assumptions. These assumptions are summarised in Table 72 and described throughout Section 5. Table 72 provides a summary of the scenario analyses conducted within the model. These scenarios explore the underlying structural uncertainty within the model based on areas where there are key data gaps or areas where alternative options are available.

Table 72: Model assumptions

Type	Assumption	Rationale
Survival data	FLAG efficacy = FLAG IDA efficacy	This is supported by a study of 105 patients with poor risk acute leukaemia or myelodysplastic syndrome that were treated over a 4-year period. This study showed no statistical difference in outcomes between FLAG and FLAG-IDA.[96] The similarities in efficacy are further supported through UK clinical expert opinion.
	Consistent with the trial, OS and PFS after HSCT are treatment-dependent.	This approach has been taken based on the clinical evidence available.
	Each of the standard of care individual treatments are assumed to have similar efficacy	UK expert clinicians indicated that the outcomes seen within the comparator arm of INO-VATE 1022 were broadly representative of UK treatments. Therefore, the same efficacy is applied to each individual drug in the comparator arm. Costs are applied respective to each comparator.
	After HSCT, in the base case it is assumed that OS curves can be extrapolated to 3 years, at which point general mortality is applied.	As HSCT is a curative therapy, with initial mortality post-transplant it is assumed that after 3 years, patients are considered cured. This is in line with prior models in similar disease areas and was supported by a UK clinician.
	It is assumed that all patients' response is determined after 1 cycle of treatment.	Simplifying assumption within the model. Given the majority of costs are applied at baseline in the model (including full course of treatment that reflects >1 cycle), this is expected to have minimal difference on the outcomes.
Adverse events	The GvHD incidence is not treatment specific.	It is assumed that GvHD is a result of HSCT itself and prior treatment would not influence this. The incidence rate of Kiehl et al. (2004) is applied in both the inotuzumab and the SoC arm.
	Treatment specific	EQ-5D instrument was used within the trial, and

Type	Assumption	Rationale
	utilities captured by the EQ-5D incorporate AEs associated with treatment.	therefore already accounts for AE disutility on-treatment.
	Disutility was applied for 1 cycle for patients encountering VOD. The methodology for this was taken from that applied within the blinatumomab SMC submission.	The assumption was made that quality of life with severe VOD was approximately the same as acute liver failure prior to a transplant. The average duration of VOD in the INO-VATE 1022 trial was 26.8 days. This may over-estimate the impact of VOD, specifically on inotuzumab patients, as it is not reflective of the benefits of defibrotide, and further, there are some patients who incur VOD on treatment while completing the EQ-5D, so the disutility is double-counted. The result is a conservative ICER for inotuzumab.
	The incidence of VOD is taken from non-Japanese patients only.	The VOD incidence was different for Japanese patients in the trial to non-Japanese. It is expected these are due to differences in Japanese clinical practice, particularly the use of conditioning regimens (ThioTEPA). To make the base case more applicable to the UK, the non-Japanese incidence was used.
Drug acquisition and administration	No resource use is incurred outside of administration and AEs	Assumed that any routine monitoring / tests would be applied to both arms within the model. In addition, these tests would likely be incorporated within other costs, e.g. administration costs or resource use associated with the occurrence of AEs.
	It is assumed that all patients who die have the end of life costs for 1 year, as per the PSSRU report.	Given the poor survival post-progression, it is assumed that the 1 year's end of life cost would be likely to include those related to progression, as this occurs near the end of life. This cost is applied to the additional patients transitioning to the death state in each cycle.
	The cost of GvHD was assumed to be €30,000, identified from the literature. This was converted to GBP and inflated to current prices (2014/2015).	A targeted literature review was conducted, where Espérou et al. was considered the most appropriate paper to include within the model, as it reported costs associated with GvHD separate to HSCT and in line with clinical opinion.
	For the treatment of VOD, we assume that defibrotide is used to treat VOD	Clinician feed back (from advisory board)[48] and previous SMC submission informed this cost. The cost applied to VOD is the average of the cost of defibrotide and the cost of the intensive care stay.[160]
Utilities	End-of-treatment utilities are applied after	The INO-VATE 1022 measured utilities during treatment. It is assumed that the end-of-

Type	Assumption	Rationale
	treatment up to disease progression or HSCT.	treatment utilities can be applied after treatment up to relapse or HSCT as it is assumed disease level is constant during this time.
	The utilities of AML patients after HSCT from Kurosawa et al. (2016) are assumed to be applicable to patients with R/R B-cell ALL after HSCT in the UK setting.	Clinical fed back suggested that these utilities were appropriate in the absence of relevant utilities from the trial, or specific R/R B-cell ALL utilities from the literature.[162] Kurosawa et al. (2016) provided utilities for up to 12 months after HSCT, for 1–2 years after HSCT, for 3–5 years after HSCT and from 5 years after HSCT. These are applied in respective cycles in the model.[161]
	The utility for *progression* states is taken from Aristides et al. (2015) and is applied up to death.	Patients would be likely to experience a lower quality of life once progressed, and therefore the on-treatment utilities captured within the INO-VATE 1022 trial may have overestimate HRQL for progressed patients. The literature informed a lower utility for these patients.

Key: AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; CRi, complete response with incomplete count recovery; FLAG, fludarabine plus cytarabine plus granulocyte-colony stimulating factor; GvHD, graft versus host disease; IDA, idarubicin; OS, overall survival; PFS, progression-free survival; SMC, Scottish Medicines Consortium; HSCT, haematopoietic stem cell transplant; SoC, standard of care; VOD, veno-occlusive disease.

5.7 Base-case results

5.7.1. Base-case incremental cost effectiveness analysis results

Base case results of the economic comparison between inotuzumab and SoC are presented using a discount rate of 1.5% for costs and QALYs over the 60-year time horizon. Results have also been reported for the discount rate 3.5% and are presented in Appendix 12. This is line with the NICE Methods Guide (as set out in Table 41 and Section 5.2.2).

As inotuzumab's benefit is bridging more patients to potentially curative therapy, much of the QALY benefit is observed in the longer run as the survival outlook for these patients changes from 'end-of-life' back to that of the normal population. As the majority of costs are experienced in the short term in the model, discounting minimally impacts on the total costs in each arm. However, as benefits are observed far into the future for more patients on inotuzumab (>30 years for the average patient who survives to the cure point), applying a higher discount rate reduces

inotuzumab's QALYs more so than any other parameter in the tables. The resulting impact to the ICER is testament to the rationale set out in the NICE Methods Guide, which comments on the large impact discounting has in the face of such longer term benefits. The impact of following the Methods Guide's advice in using a 1.5% discount rate in such circumstances is clearly demonstrated in the reduced ICER.[144] However, it is important to note how the true incremental QALY benefit is still penalised by even a lower discount rate of 1.5%.

Inotuzumab was estimated to generate an additional 5.18 life years and [redacted] QALYs in the model (ranging to [redacted] incremental QALYs when discounting at 3.5%). This represents a substantial improvement to the length and the HRQL for patients in an end-of life disease with an extremely poor prognosis. The base case results using the 1.5% discount rate are presented in Table 73, with a deterministic ICER of £40,013 per QALY. This ICER ranges to £55,869 per QALY when 3.5% discounting is applied, with the difference the result of weight given to future benefits being reduced.

Table 73: Base case results discounted at 1.5%, Inotuzumab versus SoC

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£40,013
SoC	[redacted]	[redacted]	1.49				
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.							

Table 74 presents undiscounted results over the 60-year time horizon. When results are undiscounted, the ICER for inotuzumab falls to below £30,000 per QALY.

Table 74: Base case undiscounted results, Inotuzumab versus SoC

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£29,872
SoC	[redacted]	[redacted]	1.49				
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.							

5.7.2. Clinical outcomes from the model

Table 75 summarises the median results estimated from the model in comparison to the median results obtained within the trial. As noted throughout the submission, the use of median survival in this setting is very limited due to the lack of proportional hazards within survival curves as shown in Section 4. The table shows that the modelled outcomes closely fit observed data within each of the respective health states, although the '*No CR/CRI & no HSCT'* health state appears to slightly underestimate survival in both arms compared to the observed data, while the post-HSCT slightly overestimates results. Modelled PFS outcomes are similar to the trial in both arms, with the SoC PFS matching the observed results, while PFS is slightly underestimated within the inotuzumab arm by [redacted]. For OS, both results show a slight underestimation; however, the underestimation does not favour one arm over the other, and is therefore likely to introduce little bias in favour of either treatment arm.

Table 75: Summary of median results compared to INO-VATE 1022 trial results (months, undiscounted)

	Outcome	Inotuzumab trial results	Inotuzumab model results	SoC trial results	SoC model results
Median PFS (months)	No CR/CRi	[redacted]	0.92	[redacted]	0.92
	CR/CRi & no HSCT	[redacted]	5.52	[redacted]	3.68
	Post HSCT	[redacted]	5.52	[redacted]	6.44
	Total PFS	[redacted]	4.60	[redacted]	1.84
Median OS (months)	No CR/CRi	[redacted]	2.76	[redacted]	3.68
	CR/CRi & no HSCT	[redacted]	8.28	[redacted]	7.36
	Post HSCT	[redacted]	10.12	[redacted]	15.63
	Total OS	[redacted]	6.43	[redacted]	5.52

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplant; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

As the medians provide only limited value in interpreting the data, Table 76 displays the mean outcomes. This table also includes mean OS for both arms, measured at a cut-off of 37.7 months; this is the cut-off which informed the RMST results (i.e. maximum follow-up). If the data are cut at this point, the modelled outcomes are 13.2 months for mean OS in the inotuzumab arm, and 9.9 months in the SoC arm, a difference of 3.2 months. This is closely aligned with the RMST presented in Section 4.7, where the restricted mean OS was 13.9 months in the inotuzumab arm and 9.9 months in the control arm, a difference of 3.9 months.

Table 76: Summary of mean modelled results (months, undiscounted)

Outcome (months)	Inotuzumab trial results	Inotuzumab model results	SoC trial results	SoC model results
Mean PFS	-	43.66	-	5.06
Mean OS	-	79.95	-	17.84
Restricted mean OS	13.9	13.19	9.9	9.96
Key: OS, overall survival; PFS, progression-free survival; SoC, standard of care.				

5.7.3. Disaggregated results of the base case incremental cost effectiveness analysis

Table 77 summarises the total QALYs obtained in both arms of the base case model, disaggregated based on the three model health states. Table 77 presents the total LYs accrued over the time horizon. As would be expected, the largest difference in the two treatment arms is shown in the post-HSCT health state.

Table 77: Summary of discounted QALY gain by health state, (1.5% discount rate)

Health state	QALY intervention Inotuzumab	QALY comparator SoC	Increment	Absolute increment	% absolute increment
No CR/CRi	[redacted]	[redacted]	[redacted]	[redacted]	**2.65%**
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	**2.36%**
HSCT& Post HSCT	[redacted]	[redacted]	[redacted]	[redacted]	**94.99%**
Total	[redacted]	[redacted]	[redacted]	[redacted]	**100.00%**
Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; QALY, quality-adjusted life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.					

Table 78: Summary of LY gain by health state, undiscounted

Health state	LY intervention Inotuzumab	LY comparator SoC	Increment	Absolute increment	% absolute increment
No CR/CRi	0.12	0.31	-0.20	0.20	3.52%
CR/CRi & no HSCT	0.24	0.16	0.07	0.07	1.30%
HSCT & Post HSCT	6.31	1.01	5.30	5.30	95.17%
Total	6.66	1.49		5.57	100.00%

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; LY, life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Table 79 presents the cost breakdown in each of the health states. As the model applied treatment, hospitalisation and AEs associated with treatment costs in Cycle 0 before patients respond to treatment, the majority of costs (treatment costs, administration costs, etc.) are accrued in the No CR/CRi health state, which is where patients begin the model at baseline (see Section 5.5.2).

Table 79: Base case: total discounted costs accrued in each health state (1.5% discount rate)

Health state	Total lifetime cost inotuzumab	Total lifetime cost SoC	Increment	Absolute increment	% absolute increment
No CR/CRi (includes drug acquisition cost)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR/CRi & no HSCT	£3,568	£2,325	£1,243	£1,243	[redacted]
HSCT & Post HSCT	£60,479	£26,882	£33,598	£33,598	[redacted]
Total	[redacted]	[redacted]		[redacted]	100.00%

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; LY, life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Table 80 presents the data further split by the category of cost incurred within the model.

Table 80: Base case: category of discounted costs accrued within the model (reflective of the average patient), (1.5% discount rate)

Item	Costs Inotuzumab	Costs SoC	Increment
Treatment	[redacted]	[redacted]	[redacted]
Adverse events	£13,659	£1,908	£11,751
Resource use	£2,583	£4,633	-£2,050
Associated with HSCT	£44,828	£23,761	£21,067
Subsequent induction treatments	£7,625	£19,199	-£11,574
End of life	£10,722	£11,390	-£668
Total	[redacted]	[redacted]	[redacted]
Key: HSCT, hematopoietic stem cell transplant; SoC, standard of care.			

5.8 Sensitivity analyses

5.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed within the cost-effectiveness analysis, conducted for 5,000 iterations. This analysis randomly samples parameters from within their chosen distributions. This analysis displayed the impact of parameter uncertainty within the economic model. The average (mean) incremental QALYs gained from inotuzumab across these 5,000 runs is displayed in Table 81. This resulted in a mean probabilistic ICER was £48,459 per QALY for a discount rate of 1.5%.

Table 81: Base case probabilistic ICERs, Inotuzumab versus SoC (discounted 1.5%)

	Incremental			ICER (inotuzumab vs SoC)
	Costs	QALYs	LYs	
Costs and benefits discounted at **1.5%**	[redacted]	[redacted]	4.69	£48,459
Key: ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.				

The visual results of the PSA runs are presented in Figure 54, which plot the incremental cost and QALY results at each iteration. The majority of incremental QALYs range from approximately [redacted] to [redacted], while the costs range from [redacted] to [redacted] The uncertainty of which was thoroughly explored within the PSA. The largest spread of uncertainty was across the x-axis reporting the incremental QALYs.

This spread is primarily the result of uncertainty that has been modelled around the post-HSCT OS parameters. Indeed, when these parameters are removed from the PSA, the probabilistic ICER was £42,076 per QALY, similar to the deterministic ICER (£40,013 per QALY). There are several caveats to note around the higher probabilistic ICER (£48,459 per QALY) that includes post-HSCT OS parameters, based around these being artificial constructs of the data available for modelling (as opposed to true clinical uncertainty):

- Firstly, the uncertainty seen from the post-HSCT OS is subject to small patient numbers from the trial informing these parameters. Although there is a clear plateau of the survival curves, particularly inotuzumab's, the uncertainty comes from investigating parameters that vary this plateau (i.e. vary the sustainment of longer term OS). As such, it is important to recall the assumption, validated through UK clinical expert opinion and previously investigated in the literature, that patients with longer term survival would effectively be cured past a certain point. As such, varying the plateau in the longer term OS curves is a subject of artificial uncertainty within the model, and may be at odds to the validated assumption of a cure point (*i.e.* a plateau of the curve).
- Secondly, the uncertainty may be influenced by the limited time of follow-up and censoring of data. The shape of the survival curve post-HSCT for the first 3 years post-HSCT before general population mortality is driven, in part, by the shape of the curve in the initial period post-HSCT where higher mortality may be common (*i.e.* a higher rate of mortality before the cure point). The change in mortality rate past the cure point may not be reflected in the PSA where the variance of parameters is, to a degree, related to the shape of pre-cure OS curve. Again, the result is the PSA reflecting artificial uncertainty within the model as opposed to clinical uncertainty that is observed in reality.

- Lastly, the uncertainty driving the PSA is not the result of uncertainty with the intervention, inotuzumab, or the comparator, SoC. It is uncertainty around the effectiveness of HSCT. Making a decision about the cost-effectiveness of inotuzumab based of the cost-effectiveness of HSCT, which is already used in the UK, could be considered outside the remit of this appraisal.

As set out, the uncertainty in the modelling may not extend to real life where HSCT as a procedure for ALL patients is already established and common practice. Thus, the uncertainty around longer term OS and the cause of the higher probabilistic is the result of an investigation into the efficacy of HSCT, not inotuzumab.

[redacted]

Key: ICER, incremental cost-effectiveness ratio; PSA, patient access scheme; QALY, quality-adjusted life year.

From the PSA, a cost-effectiveness acceptability curve (CEAC) was constructed. This graph shows the likelihood that each treatment is the most cost-effective option at different willingness to pay (WTP) thresholds. At a £50,000 WTP threshold, the probability that inotuzumab is a cost-effective treatment option versus SoC is 45% for a discount rate of 1.5%. The CEAC at the 1.5% discount rate is presented in Figure 55.

[redacted]

Key: SoC, standard of care.

5.8.2. Deterministic sensitivity analysis

Figure 56 presents a tornado diagram showing the parameters with the greatest impact on the ICER with the discount rate set to 1.5%, with descending sensitivity.

The ICER was most sensitive to uncertainty surrounding the cost of HSCT. This is not surprising given the large cost associated with the transplant. Other costs influencing the ICER were the inpatient stay costs and the monthly costs after HSCT. Although treatment with inotuzumab benefits patients in reaching HSCT, there is no control over the cost of HSCT (and related subsequent management costs thereafter) as these are independent. It is thus important to note that when the costs of HSCT are removed, the ICER decreases down to [redacted] per QALY in the base case for the 1.5% discount rate. As such, this may result in decision makers being influenced on whether inotuzumab is cost effective based upon the cost of an independent procedure.

In addition, the model was also sensitive to the use of subsequent induction treatments, the incidence of VOD, and the utility of progressive disease and HSCT at the cure point. The incidence of VOD impacts results through both disutility and cost

of resolving the event; however, the approach taken has resulted in the impact on the inotuzumab arm being a conservative one, in that the effect of VOD has been likely over-estimated in the model.

Figure 53: Tornado diagram displaying the 10 most influential parameters on the ICER (discounted 1.5%)

Key: ICER, incremental cost effectiveness ratio; INO, inotuzumab ozogamicin; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant; SoC, standard of care.

5.8.3. Scenario analyses

Scenarios were conducted testing both structural uncertainty within the model and parameter uncertainty. A plethora of scenarios were explored in order to fully investigate the uncertainty and thus provide as full information as possible to inform the decision makers.

Table 82 presents key scenarios analyses. These include limiting inotuzumab treatment to 3 cycles only (in line with the draft UK SPC), exploring the results of the covariate analysis when patients with no prior SCT are considered, (reflective of the UK where >1 HSCTs are not available), and changing the point at which patients are deemed ‘cured’ in the model and revert to normal population life expectancy. A further key scenario applicable to the UK was to apply utilities accepted in the blinatumomab appraisal in R/R ALL, which was recommended for use in NHS

Scotland in 2016. This scenario reduces the ICER, suggesting the base case may be using conservative estimates of utility compared to what is applicable to a UK cohort. Due to the potential relevance of these scenarios to clinical practice, results are presented both deterministically and probabilistically, as well as at both considered discount rates.

Table 82: Key scenario analyses (discounted at 1.5%)

Input	Scenario	Deterministic ICER	Probabilistic ICER*
Base case		£40,013	£48,458
Reflective of the UK clinical practice	Max 3 treatment cycles, as per SPC	£34,311	£41,610
	No prior HSCT	£37,382	£47,120
Comparator	All patients receive FLAG-IDA as SoC	£39,027	£46,993
Applying utilities from previous UK HTA in ALL	Applying utility from the blinatumomab SMC submission	£35,660	£43,106
Post HSCT cure point (base case 3 years)	2 years	£44,464	£54,723
	5 years	£39,301	£43,742
Cost of HSCT	No costs of HSCT applied	£30,576	£36,982

Key: ALL, acute lymphoblastic leukaemia; FLAG, fludarabine plus cytarabine plus granulocyte-colony stimulating factor; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; HTA, health technology assessment; SPC, summary of product characteristics; SoC, standard of care.

*Includes post-HSCT OS uncertainty

Other exploratory scenario analyses that were investigated included comparator treatment cost, time horizon, on treatment utilities, time patients receive a SCT, survival curves for OS and PFS, age adjusted utilities, dosing methods, VOD incidence rates, post HSCT cure rate, and various patient subgroups. These are presented in Table 83. Overall the model was most sensitive to the survival curve selected post-HSCT for OS within these; however, it should be recalled that the Gompertz (included in the base case) was the best suited parametric curve for post-HSCT OS, with other curves rendering poor fits, as discussed in Sections 5.3.4.3 and 5.3.5. Outside of survival parameters, the model was very sensitive to the time horizon and the discount rates selected, emphasising the need for appropriate consideration of the longer-term benefits and the use of a lower discount rate.

Table 83: Other exploratory analysis (discounted 1.5%)

Input	Base case	Scenario	ICER
Base case			£40,013
Comparator scenario	Patients split between treatments	All patients receive FLAG	£39,027
		All patients receive CM	£41,714
		All patients receive HIDAC	£42,101
Discount rate	QALYs 1.5%, Costs 1.5%	QALYs 1.5%, Costs 3.5%	£39,473
		QALYs 3.5%, Costs 3.5%	£55,869
Time horizon	60 years	5 years	£253,651
		10 years	£130,513
		20 years	£70,333
		30 years	£51,174
On treatment utility	Treatment specific utility	Pooled on treatment utilities	£40,076
Utility source after HSCT progression	Aristides et al. (2015)	Kurosawa et al. (2016)	£29,865
Time to HSCT	Tunnel states	Up to 3 cycles	£40,084
		Average time to HSCT	£37,515
Half cycle correction	Life-table method	No half-cycle correction	£40,820
Survival curve OS - No CR/CRi	Log logistic	Exponential	£39,905
		Lognormal	£39,938
		Weibull	£39,924
		Gompertz	£39,903
		Generalised gamma	£39,910
Survival curve OS - CR/CRi & no HSCT	Log logistic	Exponential	£39,796
		Lognormal	£39,960
		Weibull	£39,897
		Gompertz	£39,898
		Generalised gamma	£39,996
Survival curve OS - Post HSCT	Gompertz	Exponential	£104,414
		Lognormal	£67,248
		Weibull	£66,078
		Log logistic	£67,392
		Generalised gamma	£64,658
Survival curve PFS -	Log logistic	Exponential	£40,073

Input	Base case	Scenario	ICER
No CR/CRi		Lognormal	£40,041
		Weibull	£40,071
		Gompertz	£40,082
		Generalised gamma	£40,042
Survival curve PFS - CR/CRi & no HSCT	Lognormal	Exponential	£39,935
		Weibull	£39,997
		Gompertz	£39,994
		Log logistic	£40,040
		Generalised gamma	£40,013
Survival curve PFS - Post HSCT	Gompertz	Exponential	£74,656
		Lognormal	£32,022
		Weibull	£49,820
		Log logistic	£39,501
		Generalised gamma	£68,973
Pooled Post-HSCT	Treatment independent	Pooled Post-HSCT survival with MRD covariate	£56,819
Age adjusted utilities	No age adjustment	Age adjusted utilities applied	£43,909
Dosing method	Method of moments	Average BSA/weight including wastage	£41,230
		Average BSA/weight excluding wastage	£35,531
AE incidence of VOD	Non-Japanese patients	All patients	£40,477
Post SCT cure rate applied	3 years	1 years	£49,637
		2 years	£44,464
		4 years	£39,130
		5 years	£39,301
		Not applied	£31,299
Patient subgroup	All patients	<55 years	£37,074
		No prior HSCT	£37,382
		Salvage 1	£39,995
		Duration of prior remission ≥12 months	£32,649
		< 55 years and no prior HSCT	£34,783
		Ph+ patients	£20,836

Input	Base case	Scenario	ICER
		Ph- patients	£44,893
Utility scenario	No scenario analysis	Blincyto submission	£35,660

Key: BSA, body surface area; CR, complete response; CRi, complete response with incomplete count recovery; CM, cytarabine plus mitoxantrone; FLAG, combination of fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF); HIDAC, high dose cytarabine; OS, overall survival; PFS, progression-free survival; Ph+/-, Philadelphia chromosome positive/negative; SCT, stem cell transplant; VOD, veno-occlusive disease.

Notes: *Exponential, log-normal, gamma produce clinically implausible results as the longer term mean OS of patients post-HSCT is far greater for the standard of care chemotherapy than with inotuzumab. These curves have been presented for completeness; however, the results contradict clinical expert opinion so these scenarios are not considered relevant for decision making.

5.8.4. Summary of sensitivity analyses results

The results of the PSA indicated that the majority of uncertainty lies within the estimated QALYs (shown by the spread across the x-axis in Figure 54). However, inotuzumab provided more QALYs than SoC in over 96% of the iterations, and on average, inotuzumab offered [redacted] additional QALYs at a 1.5% discount rate. When considering the longer-term survival benefit to patients with inotuzumab through increased HSCT, the undiscounted results demonstrate an even higher QALY gain for patients with inotuzumab.

Key uncertainties within the model parameterisation shown from the OWSA were related to long-term utility, or to higher incurred costs, such as the cost of HSCT, the proportion of patients receiving blinatumomab or inotuzumab as subsequent induction treatment, etc. The utility of progressed disease patients was the largest driver, although this only varied the ICER by 5% around the base case, when tested at its lower and upper bounds.

Extensive scenario analyses were performed to explore structural and parameter uncertainty across a wide range of inputs. In general, the ICER remained stable with results consistently below the £50,000 per QALY threshold in key scenarios. Similar incremental costs and benefits were gained across key scenarios. In the exploratory scenarios, the key uncertainties were within the survival of post-HSCT patients; however, several of these scenarios can be rationally excluded due to related implausible clinical outcomes (see footnote of Table 82). It is worth noting that the benefit of HSCT as a potentially curative therapy has already been explored within

the literature and prior appraisals. Therefore, this uncertainty within the model (shown within the PSA results in Figure 54) does not necessarily extend to uncertainty in UK clinical practice (where HSCT benefit to survival is established), although it has been explored for completeness. When removing the post-HSCT OS parameters from the PSA, uncertainty was reduced, producing an average PSA ICER of £42,076 per QALY from 5,000 iterations. Removing the costs of HSCT shows that the cost of this procedure, although independent to the cost of inotuzumab, increases the ICER.

5.9 Subgroup analysis

No explicit subgroups were explored within the economic evaluation. Instead covariate analysis was conducted that explored characteristics of patients of particular interest in the R/R B-cell ALL setting. These are explored within scenario analysis reported in Section 5.8.3.

5.10 Validation

5.10.1. Validation of *de novo* cost-effectiveness analysis

The analysis uses the literature and previous appraisals to build a model structure that allows the effective application of the clinical trial evidence into the economic evaluation. A partitioned survival model that reflects R/R ALL, including progression, mortality, remission and subsequent potentially curative therapy, has been validated by multiple UK clinical experts as applicable to the decision problem.

The model input data for PFS and OS were reflective of the health state patients were in; this provided a better refection of reality using a single survival model for PFS or OS, as the pathway is more complicated than the traditional solid tumour three-state Markov model.

The outcomes of the model were validated against trial input data where available, and modelled longer term survival was in line with UK clinical expert advice in that beyond a cure point (typically between 2 to 5 years) patients could be expected to return to normal life expectancy. A wide range of one-way, probabilistic, and deterministic scenario and sensitivity analyses were presented in order to explore both structural and parameter uncertainty. Observations across these analyses

illustrate that the intervention is consistently cost-effective versus the UK standard of care.

Clinical expert consultation indicated the trial results were generalisable to the UK, however the subgroup of those with no-prior HSCT was of particular interest as currently only one HSCT is currently offered in UK practice. To further reflect on the applicability to UK practice, a scenario was also presented which limited the treatment cycles to a maximum of 3, in line with the draft SPC. In both this subgroup and this scenario analysis the ICER falls, indicating the base case is likely a conservative estimate of inotuzumab's true cost-effectiveness to the NHS.

5.10.2. Quality control

Several quality control measures were undertaken to validate the model findings included in this submission. Internal quality control was undertaken by the developers of the model on behalf of the manufacturer. In addition, an independent modeller critiqued the structure, parameter inputs, and core assumptions. Simplistic crude modelling was also undertaken that showed that the estimates of costs and QALYs were intuitive.

5.11 Interpretation and conclusions of economic evidence

B-cell ALL is a rare and frequently fatal leukaemia. It is a disease diagnosed across all age groups and in the R/R setting affords a median life expectancy as low as 3 months, with a mean closer to 1 year, should patients be able to benefit from potentially curative therapy such as HSCT. The R/R population is an orphan population, with only 117 adults expecting to present each year. There is a lack of clear guidance on treatment options for these patients, but with the currently available treatments long-term disease-free survival after initial treatment is achieved only in a minority of adult patients currently.[40] It is important to note that in UK standard practice HSCT is only possible in patients with no active disease, meaning that with the limited success of current treatments few patients are able to access potentially curative therapy.[14] Therefore, due to the rarity of the disease, high relapse rates, poor survival outcomes and a lack of clear guidance on treatment options for these patients, there is a substantial unmet need for adult patients with R/R B-cell ALL.

Given the demonstrable unmet need, inotuzumab represents an important treatment for R/R B-cell ALL and a major step change in the management of the disease. Inotuzumab is not only associated with much higher rates of CR/CRi than the current standard of care, but also with a statistically significant and clinically meaningful improvement in MRD negativity, an important prognostic indicator for ALL correlating with improved long-term survival outcomes.[17, 45] Importantly, inotuzumab allows significantly more patients to progress to potentially curative therapy), which was demonstrated in the clinical trial with HSCT (see Section 4.7). Inotuzumab's ability to bridge an increased number of patients to such therapy has a substantial impact on mean OS, and potential, long-term improvements in patients' HRQL. This improvement is even more apparent when the conservative longer-term utilities were replaced with those identified elsewhere in the literature and also those used in a recent UK appraisal in R/R ALL, with the ICER falling in these scenarios.

5.11.1. Comparison of the economic evaluation with published economic literature

This is the first economic evaluation that focusses on assessing the cost effectiveness of inotuzumab with standard of care treatments for patients with R/R B-Cell ALL. No study assessing the cost-effectiveness of inotuzumab was identified within the economic SLR, and therefore, it was not possible to compare the outcomes of the economic model developed for this submission with any existing literature focussing on the same decision problem.

5.11.2. Generalisability of the economic evaluation to the UK

The population included in the economic evaluation was consistent with the anticipated licence of inotuzumab. The economic evaluation reflects the patients enrolled within the INO-VATE 1022 study and is relevant to all patients who would be eligible for treatment with inotuzumab within a UK setting. As the INO-VATE 1022 trial was initiated across 193 centres in 25 countries (129 centres screened or treated at least 1 patient), there is a chance that some differences would be seen in treatment across the different centres, mainly related to the criteria for HSCT eligibility. Despite this, UK clinical expert opinion was sought on the generalisability of the trial and the outcomes were regarded as that which would be expected in UK patients, and thus applicable to the NHS. To be thorough, UK clinician expert opinion

was also sought to gauge the most important patient characteristics appropriate to determine patient outcomes in a UK setting. From this input, covariate analysis was conducted as part of the survival analysis, in order to allow the cost-effectiveness model to explore economic outcomes more relevant to the UK population, e.g. patients who have not had a prior HSCT, given that a second HSCT is not currently reimbursed in the UK.

All costs within the model were applied from a UK perspective and where possible were derived from recommended UK sources. HRQL for on-treatment utilities were obtained within the trial and the literature was used to inform post-HSCT utilities. These were validated by UK clinicians and seen as the best source of evidence in the absence trial data.

Extensive sensitivity analyses were conducted to explore both parametric and structural uncertainty within the economic model. This involved probabilistic sensitivity analyses, OWSAs, and scenario analyses exploring alternative approaches to modelling, including the extrapolation techniques described through Section 5.3.

The OS projections for the INO-VATE 1022 trial were validated by UK clinical experts, and the modelled outcomes were compared to the results within INO-VATE and existing sources available relevant to the SoC arm. The modelled median results were very similar to those seen within the trial.

5.11.3. Strengths and weaknesses of the economic evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model. Phase III data from the INO-VATE 1022 trial comparing inotuzumab to investigators choice were used to inform survival (extrapolated using parametric survival curves), remission rates, AE rates and HRQL within the model.

The economic model was consistent with the disease pathway and based around a patient's remission status and whether they achieved HSCT, currently the only available potentially curative treatment available for R/R B-cell ALL patients in the UK. For those patients that reached HSCT, parametric curves were fit to the data and extrapolated. If alive 3 years post-HSCT, patients were considered 'cured' and subsequently followed general population mortality, an approach taken in prior economic models in similar disease areas and validated through UK clinical expert

opinion. For patients not undergoing HSCT, parametric survival curves were fit to the data based upon whether or not patients achieved CR/CRi.

There are some limitations that should be noted within the economic evaluation. As acknowledged, the model incorporates the best available evidence for the R/R B-cell ALL population: using the INO-VATE 1022 trial data provides the largest evidence base available for inotuzumab with 326 patients enrolled in the trial (with 307 used in the economic analysis as outlined in Section 5.3), which is a large evidence base, particularly for an orphan disease. Nonetheless, in some instances there are small patient numbers used to inform the parametric survival curves with the covariate adjustments. Given the treatment pathway, the model structure, and the large difference in the CR/CRi rates between inotuzumab and the SoC arm, the data are split, which means that parametric curves are fit to the data based on small numbers in certain groups. While parameters informed from low patient numbers have limitations, and the results of exploring the covariate analyses groups should be interpreted with caution, the uncertainty around survival was fully explored in probabilistic sensitivity analysis involving a plethora of parameters, and 5,000 iterations were conducted to explore this uncertainty rigorously.

5.11.4. Interpretation of economic evidence

The clinical effectiveness of inotuzumab translates into cost-effectiveness at a willingness-to-pay threshold of £50,000 per QALY, even after uncertainty is explored in both the structure and the parameters in the economic model. The base case deterministic ICER was £40,013 per QALY (ranging to £55,869 depending on discount rate), whilst the mean probabilistic base case ICER was comparable to the deterministic (£42,076 per QALY), ranging to £48,459 per QALY when post-HSCT OS is included within the uncertainty analyses. Key scenarios applicable to the UK showed the deterministic ICER for inotuzumab fell to between £34,311 and £39,027 per QALY, indicating the base case is likely to be a conservative estimate of the cost-effectiveness of inotuzumab when used within the NHS in England and Wales.

There are currently no targeted treatment options available for patients with R/R ALL and no targeted treatment options available for patients with Ph- B-cell ALL, with current options limited to chemotherapy, which is also associated with burdensome prolonged inpatient administrations together with high levels of toxicity. Inotuzumab

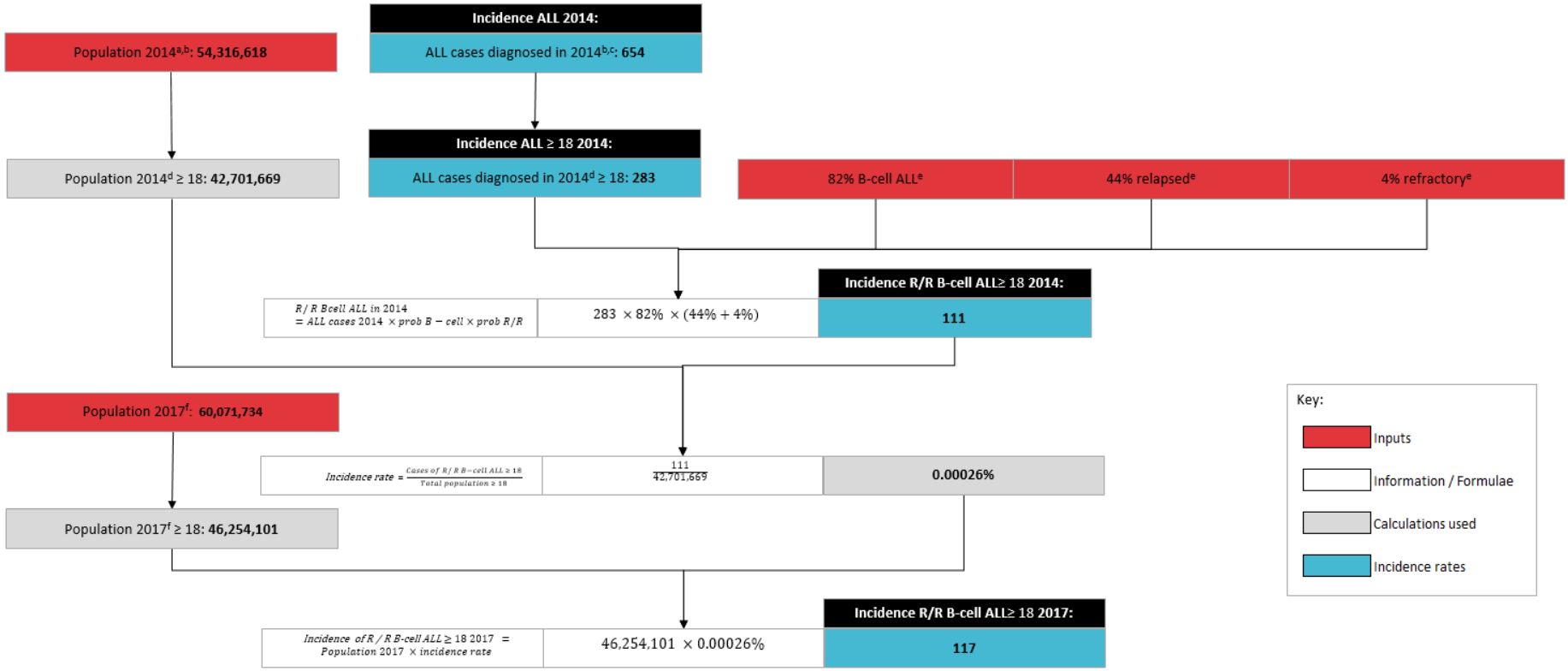
is both clinically effective versus the current standard of care, and cost effective when appraised as an end-of life medicine. The introduction of inotuzumab in the NHS will significantly improve outcomes for this small patient population, essentially curing a proportion of these patients, whilst offering value for money in the process of doing so.

6. Assessment of factors relevant to the NHS and other parties

Inotuzumab is indicated for adult patients with R/R B-cell ALL. The incidence of R/R B-cell ALL was calculated using the newly diagnosed ALL cases in 2014 from the Office of National Statistics (ONS)[184] and multiplying by the probabilities of relapsed ALL, refractory ALL and patients with B-cell ALL from Fielding et al. (2007).[41] This paper examines the outcomes of 609 adults with recurring ALL and reports that 62 out of the 1,508 patients eligible for the trial failed to achieve remission and that 609 out of 1,372 patients who entered remission relapsed within 11 months. These rates are used to calculate the proportion of patients from the newly diagnosed ALL patients who are relapsed or refractory (44% and 4%, respectively).[41] Furthermore, 409 patients were B-cell and 92 were T-cell; this proportion (82%) was used to calculate the proportion of R/R ALL who were B-cell ALL patients. The data were split by gender and age groups, and the incidence rate was calculated by comparing the incidence population of R/R B-cell ALL against the population of England in 2014 from ONS for each age/gender subset.[185]

Patient numbers were generated using these incidence rates multiplied by the population of England and Wales for 2017 up to 2021 from the ONS.[186] A brief summary diagram of how the incidence numbers were calculated it presented in Figure 57. For the budget impact, only incidence patients have been considered due to the prognosis of R/R B-ALL patients. Table 84 summarises the incidence patients used in the budget impact model.

Figure 54: Flow diagram of incidence numbers used to inform the budget impact



References: [a]; ONS 2015, [c]; ONS 2016, [e]; Fielding 2017 [f]; ONS 2014
Notes: [b]; Populations were split into 18 age groups and incidence rates were estimated specific to each group, [d]; it was assumed that ages 18-19 take up 40% of the 15-19 age group

Table 84: Incidence of R/R B-cell ALL 2017–2021

Incidence	2017	2018	2019	2020	2021
Females	47	48	48	49	49
Males	69	70	71	72	72
Total	117	118	119	120	122
Key: ALL, acute lymphoblastic leukaemia; R/R, relapsed or refractory.					

The total number of eligible patients for inotuzumab was calculated using the incidence patients for each year of treatment (Table 85).

Table 85: Total eligible patient population

Year of treatment	2017	2018	2019	2020	2021
1st year	117	118	119	120	122
2nd year	0	117	118	119	120
3rd year	0	0	117	118	119
4th year	0	0	0	117	118
5th year	0	0	0	0	117

Two scenarios were investigated for the budget impact model; the first estimates current market shares of various treatments available for R/R B-cell ALL patients in England & Wales based on clinical opinion (current market shares), and the second used the predicted market shares of these treatments including inotuzumab when this is available (future impact with inotuzumab).

The future market shares of inotuzumab are based on forecasted patient numbers for each year based on a population of 314 ALL patients. These patient numbers were used to estimate the future market share of inotuzumab over the next 5 years.

Table 86: Forecasted patient numbers receiving inotuzumab

Year	Patient numbers	Proportion of total ALL patients
2017	[redacted]	[redacted]
2018	[redacted]	[redacted]
2019	[redacted]	[redacted]
2020	[redacted]	[redacted]
2021	[redacted]	[redacted]
Key: ALL, acute lymphoblastic leukemia.		

The future market shares of the other treatments used the same proportions as the estimated current market shares but were scaled so that the total market share including inotuzumab was 100%. These market shares are presented in Table 87 and Table 88, respectively.

Table 87: Market shares of current treatment (without inotuzumab)

Treatment	2017	2018	2019	2020	2021
FLAG-IDA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyper CVAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clofarabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-drug chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	100.0%	100.0%	100.0%	100.0%	100.0%
Key: CVAD, cyclophosphamide, vincristine, Adriamycin, dexamethasone; FLAG, combination of fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF); IDA, idarubicin.					

Table 88: Predicted future market shares

Treatment	2017	2018	2019	2020	2021

Treatment	2017	2018	2019	2020	2021
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FLAG-IDA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyper CVAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clofarabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-drug chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	100.0%	100.0%	100.0%	100.0%	100.0%

Key: CVAD, cyclophosphamide, vincristine, adriamycin, dexamethasone; FLAG, combination of fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF); IDA, idarubicin.

Costs relating to treatment, AEs, resource use, post HSCT, subsequent induction treatment and end of life were taken from the model for each health state ('*No CR/CRi & no HSCT' 'CR/CRi & no HSCT', 'HSCT & Post-HSCT'*) for each year over 5 years. The scenario using current market shares used the SoC arm costs to inform the efficacy of these patients. The scenario using the future market shares were split between the inotuzumab arm costs (for the proportion who would have inotuzumab) and the SoC arm costs (for the proportion who would use the comparator treatments). The eligible patient population shown in Table 85 were multiplied by these costs, and the two scenarios were compared to see the budget impact of introducing inotuzumab.

Table 89 summarises the results of the budget impact of each scenario and the difference over 5 years.

Table 89: Budget impact of inotuzumab

Year	Current market shares (without inotuzumab)	Future market shares with introduction inotuzumab	Incremental impact	Cumulative impact

Year	Current market shares (without inotuzumab)	Future market shares with introduction inotuzumab	Incremental impact	Cumulative impact
2017	[redacted]	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	

Figure 55: Cumulative and total budget impact of inotuzumab

The budget impact of inotuzumab starts at [redacted] Year 1 increasing to [redacted] Year 5, with a cumulative budget impact of [redacted] the 5 years.

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186. Office of National Statistics (ONS). Population Estimates for UK, England and Wales, Scotland and Northern Ireland. 2016. Available

at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland Accessed: 26 January 2017.

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Level 1A
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Manchester
M1 4BT
United Kingdom

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Single technology appraisal

Leukaemia (acute lymphoblastic, B-cell, relapsed, refractory) - inotuzumab ozogamicin [ID893]

Dear Pfizer,

The Evidence Review Group, Centre for Reviews and Dissemination
University of York and the technical team at NICE have looked at the submission received on 8 February 2017 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on Friday 17 March 2017. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Tucker Technical Lead helen.tucker@nice.org.uk. Any procedural questions should be addressed to Stephanie Yates Project Manager stephanie.yates@nice.org.uk.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Further study reports required

A1. **Priority question:** Please confirm the date that the final overall survival and safety updates from INO-VATE 1022 are expected (stated in submission as expected March 2017).

Decision problem

A2. In the INO-VATE 1022 trial, only patients who could tolerate chemotherapy were eligible for inclusion. Please clarify whether inotuzumab is only intended for use in patients who can tolerate chemotherapy/potentially curative therapy (such as haematopoietic stem cell transplant (HSCT) in clinical practice, or would patients being treated with palliative intent also be eligible for inotuzumab in NHS practice?

A3. Please comment on the potential implications of the new NHS England Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (Reference: NHS England: 16068/P) on this submission, and potential implications for inotuzumab use in NHS practice.

A4. Please provide further justification for the exclusion of clofarabine and tyrosine kinase inhibitors (TKIs) alone from the decision problem, since both of these treatments are used in current NHS practice.

Systematic review

A5. Please explain why the inclusion criteria for the systematic review were broader than those for the submission. Please provide the narrower eligibility criteria that were used for the submission, as well as details of the 4 RCTs that were excluded for not having a relevant treatment comparison and the 12 non-RCTs that were of interventions other than inotuzumab. Please confirm whether any excluded studies could have informed this submission, for example used in indirect comparisons, or for providing control group data.

A6. The eligibility criteria for the systematic review states that studies will not be excluded on the basis of language. However, in the PRISMA diagram (Figure 7 on page 69) two studies were excluded as 'Non-English'. Please explain this inconsistency. In

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addition, please provide further details for the two studies excluded as 'Not retrieved' – does this mean that full text articles were unavailable?

INO-VATE 1022 trial

A7. **Priority question:** Please check the table below and correct any errors/add missing data that are available. Please also provide the same data for the ITT218 population.

Status	Inotuzumab (n=164)	Standard of Care (n=162)
Remission outcomes		
Achieved CR	55 (33.5%)	26 (16%)
Achieved CRi	65 (39.6%)	24 (14.8%)
Achieved CR or CRi	120 (73.2%)	50 (30.9%)
MRD negativity in CR/CRi patients	92/120 (76.7%)	19/50 (38%)
HSCT		
Did not have HSCT	93 [2 yr survival 8.7%]	144 [2 yr survival NR]
Achieved CR/CRi	?	?
Did not achieve CR/CRi	36 (22%)	?
Had HSCT	71 (43.3%)	18 (11.1%)
HSCT and CR/CRi	? [2 yr survival 40.5%]	? [2 yr survival 27.2%]
HSCT but not CR/CRi	8 (4.9%)	12

A8. Please provide formal test evidence of non-proportionality in the overall survival data. In addition, please provide further justification for the choice of timepoint in the RMST analysis (37.7 months). Please also provide analyses at other timepoints, e.g. 12 months and 18 months.

A9. Please confirm whether patients who received HSCT were removed from the duration of remission (DoR) analyses or censored.

A10. Please provide standard 2-sided p-values and 95% CI throughout (where 1-sided p-values and 97.5% CI have been used).

A11. **Priority question:** Please provide information on adverse event related deaths.

A12. Please provide further information on the outcomes and characteristics of the 22 patients who had veno-occlusive liver disease (VOD);please clarify which country these patients were from, the number of VOD patients that received dual alkylator conditioning, the number of VOD patients that were aged 55 years or over, and the number of VOD patients who had received prior HSCT.

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A13. **Priority question:** Please confirm whether the adverse events reported for the safety population (n=143 in standard of care [SoC] arm) for 'all cycles' included adverse events from subsequent medications received (i.e. not just FLAG-based chemotherapy, cytarabine plus mitoxantrone (CM) and high dose cytarabine (HIDAC), as presented in Table 15. Please also provide information on the number of cycles received in the SoC group, and cycle length.

A14. Please provide further information about treatment discontinuations due to study-drug toxicity. In addition, please provide details of dose reductions and temporary discontinuations.

A15. Please provide further information on the reasons why patients dropped out of the trial/withdrew consent prior to receiving treatment in the SoC arm (19 patients), if known. Please also provide baseline characteristics of these 19 patients and details of subsequent medications received. Please confirm whether follow-up data were collected/analysed for these patients. On page 85 of the submission, it states that sensitivity analyses were conducted excluding these patients, with results consistent with the overall analysis. Please provide the results of the sensitivity analyses.

A16. **Priority question:** Please provide the reasons why a proportion of patients who achieved complete remission (CR) / complete remission with incomplete haematologic recovery (CRi) did not have HSCT, for both the inotuzumab group and the SoC group.

A17. **Priority question:** Please provide justification/further information why 20 patients had HSCT without achieving CR/CRi.

A18. Please provide further information about the analyses undertaken for the patient reported outcomes (Table 29 on page 114). If possible, please present the EORTC QLQ-C30 individual scores and EQ-5D and EQ-VAS scores for the inotuzumab group and the SoC group, at the end of each treatment cycle (along with the number of patients who completed the questionnaires in each treatment group at the end of each cycle), along with the change from baseline scores and p-values. In addition, please indicate whether any treatment-time interactions were statistically significant.

A19. The ERG has received clinical advice which considered that patients would receive the first cycle of inotuzumab in an inpatient setting. Please provide data on the number of patients who were treated on an inpatient basis, rather than outpatient basis in the inotuzumab group by treatment cycle. Please discuss the generalisability to clinical practice in England.

A20. Table 9 on page 39 of the Appendices presents subgroup data suggesting better OS results for patients from North America. Table 11 on page 40 presents subgroup data, suggesting that progression free survival results may be better for patients from

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the European Union. Please provide further details to allow the ERG to assess these differences, e.g. did different regions use different comparators, different rates of HSCT, different population characteristics?

A21. Please confirm whether the full ITT population, in addition to the ITT218 population (the first 218 randomised patients), had CR/CRi assessments reviewed by an independent Endpoint Adjudication Committee.

Non-randomised evidence

A22. **Priority question**: Please provide baseline characteristics for patients included in the non-RCT studies.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival and overall survival for the following:

(i) Figures 8 (page 95) and 9 (page 98) are reported for the ITT population. Please provide similar figures for the safety population.

(ii) Figure 26 (page 174) – please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

(iii) Figure 27 (page 175) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

(iv) Figure 32 (page 179) – please provide an additional figure including number of patients at risk at each time point.

(v) Figure 33 (page 180) – please provide an additional figure including number of patients at risk at each time point.

(vi) Figure 38 (page 187) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

(vii) Figure 39 (page 187) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

B2. **Priority question**: Please provide additional Kaplan-Meier curves comparing inotuzumab and SoC (with the number of patients at risk at each time point) for progression free survival and overall survival in post-HSCT-patients. Specifically,

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please provide separate figures for: (i) CR/CRi & post-HSCT patients and (ii) no CR/CRi & post-HSCT patients. Please provide the figures for the safety and ITT population.

B3. **Priority question**: Please present additional Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival and overall survival for all post-HSCT patients (i.e. pooling the inotuzumab and SOC patients). Please provide the figures for the safety and ITT population.

B4. **Priority question**: Please incorporate additional functionality in the Excel model to incorporate the requested pooled post-HSCT patient analysis (clarification point B3) and present results for a separate scenario in the cost-effectiveness analyses based on this – including deterministic and probabilistic estimates assuming: (i) 3.5% discount rate for costs and outcomes and (ii) 1.5% discount rate for costs and outcomes.

B5. **Priority question**: The methods used to deal with non-proportional hazards do not appear conventional and also appear potentially inconsistent (i.e. shape and scale parameters are not modelled the same way). Please provide further justification for this approach and the appropriateness of this method compared to more conventional alternatives (e.g. independent functions) or utilising as much as the Kaplan-Meier data as possible.

B6. **Priority question**: Please present additional analyses to further support the appropriateness and validity of this of this approach (relating to query B5), including:

(i) Please present estimates of restricted mean survival time (RMST) for progression free survival and overall survival for each of the 3 subpopulations (No CR/CRi, CR/CRi and no HSCT and Post HSCT) based on the following time points: 12, 18, 24 and 36 months.

(ii) Please provide further evidence to support the appropriateness of including a treatment effect on the shape parameter in the selected regressions (e.g. provide formal tests such as testing for a constant time ratio or proportional odds).

(iii) Please provide further justification for only including treatment as a covariate (but not other covariates) on the shape parameter.

B7. **Priority Question:** Please provide additional clinical evidence to support the “cure point” of 3-years used in the model and the assumptions employed beyond this time point.

(i) Several clinical studies have reported lower long-term survival after allogenic HSCT (e.g. Wingard et al, Journal of Clinical Oncology, 2011; Bhatia et al, Blood,

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2007) compared to the general population. Please discuss the generalisability of these studies and any implications for the current assumptions in the company model.

(ii) Please clarify whether evidence of longer term mortality following HSCT was systematically considered within any of the reviews in the company submission.

(iii) Please incorporate additional flexibility in the Excel model to allow a higher standardised mortality ratio to be applied in the post-cure period compared to the general population. Please provide additional scenarios for the cost-effectiveness results based on assuming higher standardised mortality ratio rates and with reference to existing clinical literature.

B8. Please provide further justification for incorporating additional costs but no additional benefits for: (i) FLAG-IDA (fludarabine, cytarabine and granulocyte-colony stimulating factor plus idarubicin) vs FLAG alone; (ii) TKI (imatinib) – in patients with Ph+ disease only. Present an additional scenario analysis assuming the costs of FLAG alone and excluding TKI costs.

B9. The acquisition cost and funding status of several therapies assumed for subsequent induction treatments appears uncertain. Please present an additional scenario analysis assuming where the costs applied for patients receiving blinatumomab and inotuzumab are replaced with the costs of chemotherapy.

B10. The “end of life” costs applied in the model appear specific to cancer patients over their last 12 months of life. Please provide further justification for the appropriateness of this estimate applied in the pre and post-cure periods (i.e. whether it is reasonable to apply costs derived over a 12 month period given the short life expectancy of many patients and whether it is appropriate to assign cancer costs to mortality events in the post-cure period).

B11. Please provide further clarification regarding how the post-HSCT utility values were derived from the reference provided (Kurosawa, 2015).

B12. The costs sheet in cell E101 (“Outpatient: Deliver Complex Chemotherapy”) references SB13Z NHS Reference Costs 15/16. Please confirm whether this is the correct reference or whether this should refer to SB14Z? The ERG have not been able to validate this unit cost estimate based on checks of the Reference Costs. Please confirm that the correct unit cost has been applied.

B13. **Priority question**: Please confirm whether the acquisition cost for inotuzumab stated in the company submission is the final list price.

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Section C: Textual clarifications and additional points

C1. **Priority question:** On page 116 of the company submission it states that the only groups which did not display significant rate differences were for patients with Philadelphia chromosome positive (Ph+) disease and patients with chromosome translocation (4:11) positive disease. Please clarify whether this statement is referring to Figure 15 on page 116 or Figure 16 on page 118. In addition, please present a commentary and p-values for Figure 16.

C2. **Priority question:** On page 109 it states that baseline pain scores favoured inotuzumab, but in Table 28 (page 110) pain scores are identical in the inotuzumab and SOC group. Please clarify whether the figures in Table 28 are correct.

C3. Page 80 describes the competing risk analysis. Please confirm whether the category 'death due to other causes' (excluding relapsed or refractory [R/R] B-cell ALL) also excluded death due to VOD and other adverse events of treatment for R/R B-cell ALL.

C4. The Advisory Board in the R/R B-Cell ALL report is referenced throughout the company submission. The names, roles and expertise of experts at the advisory board meeting have been removed. Please provide details of the expertise of the advisors, so that the ERG can assess the reliability/applicability of this report.

C5. Please explain why adverse event results for stomatitis and dyspepsia are reported as 'not applicable' for 'all cycles' in Table 33 on page 132.

C6. Please explain apparent inconsistencies in patient numbers between Tables 22 and 23 (pages 100 and 101) (e.g. 22 minimal residual disease [MRD]+ vs 41 MRD+, 92 MRD- vs 97 MRD- for inotuzumab group, and similar inconsistencies in the SoC group).

C7. Please clarify whether there is a typographical error in Table 13. The total number of treated patients in the SoC group = 1 + 128 + 15 = 144, however the total SoC population = 143.

C8. Please clarify whether there are any inconsistencies between Figures 14 and 15 on page 116 and Table 14 on page 88.

Searching

C9. Please clarify whether any trial registers were searched for ongoing or recently completed trials of inotuzumab ozogamicin or the other drugs used to treat ALL listed in table 8, on page 65. If so, please provide details of which trial registers were searched, the date of the search and the search strategy used.

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C10. It is stated that an English language limit has been applied to the searches of MEDLINE and Embase in Appendix 2, Table 1, page 8 at line 43, giving 7856 results. However section 4.1.1., page 63 of the company submission states that studies published in non-English languages were included in the systematic literature review and flagged. Please clarify which statement is correct and also whether studies published in non-English languages where included in the cost-effectiveness searches, reported in Appendix 3.

C11. In the PRISMA flow diagram on page 68, 8554 records are reported as identified through the database searching. The 8554 results reported suggests that the search results from MEDLINE and Embase had an English language limit applied. Please clarify that 8554 the correct figure for the results identified through database searching. Should it be higher than this if any non-English language results were identified and were then screened for possible inclusion in the review? Please also clarify whether studies published in non-English languages where include for the cost-effectiveness searches, reported on page 154

C12. Please provide details of the source for the study design search filters used in Table 1, pages 7-8, (search lines 34 and 35) in Appendix 2?

C13. The title of Appendix 2 refers to identifying safety and health-related quality of life data as well as clinical effectiveness data. Please clarify whether this is correct?

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Single technology appraisal

Leukaemia (acute lymphoblastic, B-cell, relapsed, refractory) - inotuzumab ozogamicin [ID893]

Dear Dr Sutcliffe,

We have received an unprecedented high number of clarification questions for this appraisal and want to provide below a summary of our key comments that we believe should be noted by the Evidence Review Group and the NICE Appraisal Committee in the consideration of these new evidence datasets.

We would like to highlight that we included a number of scenarios in our submission to address uncertainties and ensure the evidence was as clear and transparent as possible. In order to aid decision making, we attempted to explore the data and the assumptions behind the model in over 60 scenarios and sensitivity analyses, which consistently found inotuzumab to have an ICER below the willingness-to-pay threshold of £50,000/QALY in section 5.8 of the submission.

Whilst we appreciate the ERG's objective to explore the uncertainties within the data, we are unclear on the clinical and economic rationale behind some of the requests for additional data given the plethora of scenario analyses originally provided in our submission. Of particular concern to Pfizer is question B4 on the pooling of overall survival post-HSCT and question B7 on the estimates of lower longer term mortality rates post-HSCT**.**

In question B4, simply pooling the data not only abandons the available randomised, controlled evidence past the point of transplantation it also fails to account for prognostic factors associated with OS that may differ by treatment, notably minimal residual disease (MRD) negativity. This was shown to be statistically significantly different between the two treatment arms in the trial [1] (page 187 in submission) and also accounted for in the scenario analysis presented in Table 85 (page 256) of our submission. Therefore, the alternative scenario analyses should be interpreted with extreme caution as we believe that they are neither appropriate nor clinically plausible and will lead to an extremely biased estimate of cost effectiveness.

In question B7 (i), due to the paucity of recent evidence on long term survival post the cure point, adjustments to the longer term mortality rate can be considered somewhat arbitrary and should be considered with caution. As a result of improvements in mortality rate over time,

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already considered “excellent” in the literature (add references), it is reasonable to assume that long term mortality rates would not differ greatly for patients surviving post-HSCT compared to the general population once past the cure point. Despite this positive long term outlook, it should be noted that reduced utilities were included in the base case as a result of patients experiencing comorbidities or progressing in the model, which is both clinically plausible and more conservative than other modelling approaches taken in ALL.

Please note, Pfizer is unable to provide responses to the questions A7, A19, B5, B6 and C1 at this time. The response to B5, that informs B6 (ii, iii), required clarification from the ERG, which was received on 16 March. The response to these questions will therefore be provided by 22 March. The responses to A7, A19, B6 (i) and C1 require additional data programming and/or review by our statistical team. Responses to these questions will therefore be provided on or before 27 March.

Pfizer are happy to further address any other areas requiring additional clarity with the ERG and the NICE Technical Team ahead of the first Appraisal Committee meeting.

With kind regards,

[redacted]
Oncology Lead, Pfizer Ltd.

References

1. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *New England Journal of Medicine*. 2016; 375(8):740-53.

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Section A: Clarification on effectiveness data

Further study reports required

A1. **Priority question:** Please confirm the date that the final overall survival and safety updates from INO-VATE 1022 are expected (stated in submission as expected March 2017).

[redacted]

References

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SUPPORTING DOCUMENTATION

None

Decision problem

A2. In the INO-VATE 1022 trial, only patients who could tolerate chemotherapy were eligible for inclusion. Please clarify whether inotuzumab is only intended for use in patients who can tolerate chemotherapy/potentially curative therapy (such as haematopoietic stem cell transplant (HSCT) in clinical practice, or would patients being treated with palliative intent also be eligible for inotuzumab in NHS practice?

Pfizer response:

In the proposed draft label, inotuzumab ozogamicin is not only intended for use in patients who can tolerate chemotherapy or proceed to potentially curative therapy (e.g., hematopoietic stem cell transplant [HSCT]). However, patients being treated with palliative intent (e.g., patients receiving steroids, pain control, etc.) would not be expected to receive inotuzumab ozogamicin in NHS practice.

Patients able to tolerate chemotherapy

In Study B1931022, only patients who could tolerate chemotherapy were eligible for inclusion since the study was designed to randomize patients (1:1) to receive inotuzumab ozogamicin or chemotherapy; therefore, at the study outset all patients had to be eligible to receive chemotherapy since they had a 50% chance of being randomized to this study arm. However, the indication for inotuzumab ozogamicin will not be restricted to patients who can tolerate chemotherapy.

Patients able to proceed to HSCT

In Study B1931022, patients were eligible to receive treatment with inotuzumab ozogamicin regardless of whether they were eligible to proceed to HSCT. Typically, patients should achieve CR or CRi before proceeding to HSCT; however, not all patients who achieved and remained in remission proceeded to HSCT in Study B1931022. Although the reasons for not proceeding to HSCT were not formally collected in Study B1931022, in general, reasons why patients don't proceed to HSCT include unsuitability for conditioning chemotherapy, lack of donor availability, older age, etc.

In Study B1931022, HSCT after treatment with inotuzumab ozogamicin was associated with a lower risk of death compared to no HSCT (Study B1931022 sCSR Table 14.2.2.7.9). However, while a follow-up HSCT after treatment with inotuzumab ozogamicin was associated with an

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improved overall survival, patients not proceeding to HSCT were also able to benefit from treatment. As of the 08 March 2017 cut-off date, in the inotuzumab ozogamicin arm, 29 patients had OS >18 months; of these, 24 patients had a follow-up HSCT and 5 patients did not have a follow-up HSCT (Study B1931022 Table 530.186.3; Study B1931022 Table 530.186.4).

SUPPORTING DOCUMENTATION

Study B1931022 sCSR Table 14.2.2.7.9

Study B1931022 Table 530.186.3

Study B1931022 Table 530.186.4

A3. Please comment on the potential implications of the new NHS England Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (Reference: NHS England: 16068/P) on this submission, and potential implications for inotuzumab use in NHS practice.

Pfizer response:

The INO-VATE 1022 trial shows that inotuzumab can be used in patients prior to 1st HSCT or prior to subsequent HSCT. Based on the INO-VATE 1022 trial, for prior/no prior HSCT status, inotuzumab is consistently efficacious across different subgroups (as shown in Figure 15 in the company submission). [redacted], for inotuzumab and SOC, respectively. CR/CRi rates for no prior transplantation were [redacted], for inotuzumab and SoC, respectively.

From an economic perspective, the base case ICER is reflective of all patients (1st and 2nd HSCT) and is cost-effective (£40,013/QALY). Therefore inotuzumab remains a cost effective use of NHS resources R/R ALL patients following 1st HSCT or 2nd HSCT.

Pfizer is not able to comment on the number of patients that would proceed to 2nd transplant following the recent change to the policy.

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A4. Please provide further justification for the exclusion of clofarabine and tyrosine kinase inhibitors (TKIs) alone from the decision problem, since both of these treatments are used in current NHS practice.

Pfizer response:

Clofarabine is licenced for patients up to age 21, with the SPC stating that there are insufficient data to establish safety and efficacy in adult patients [1]. Key clinical expert opinion has indicated that clofarabine is commonly used in younger patients; it is suggested that there is an estimated 10–15% off-label use in 18–30 year olds in the UK. With under 30s likely to constitute less than 30% of the expected eligible population for inotuzumab, clofarabine usage alone would equate to less than 5% of the whole adult population. Therefore, as it is not the standard of care relevant to this decision problem, it has not been considered a comparator in the economic evaluation. Furthermore, as this use is off-label, it is not appropriate to compare to inotuzumab within this submission.

TKIs alone (without associated chemotherapy) would likely have similar efficacy to treatment used in palliative care [2], therefore TKIs alone would not be a viable route to HSCT. It is more likely that TKIs would be used in combination with chemotherapy (as standard of care) in a subgroup of Ph+ patients. Tyrosine kinase inhibitors (TKIs) were included as a comparator for Ph+ patients in combination with the chemotherapy selected as SoC in line with the final scope shown in Table 1 of the submission.

References

[1]Sanofi. Summary of Product Characteristics. Evoltra: 1mg/ml concentrate for solution for infusion. 28 September. Available at: http://www.medicines.org.uk/emc/medicine/18023/SPC/Evoltra+1mg+ml+concentrate+for+solution+for+infusion Accessed: 9 December 2016.

[2] Ponatanib Appraisal Consultation Document. https://www.nice.org.uk/guidance/GID-TA10060/documents/appraisal-consultation-document. Accessed: 14 March 2017

Systematic review

A5. Please explain why the inclusion criteria for the systematic review were broader than those for the submission. Please provide the narrower eligibility criteria that were used for the submission, as well as details of the 4 RCTs that were excluded for not having a

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relevant treatment comparison and the 12 non-RCTs that were of interventions other than inotuzumab. Please confirm whether any excluded studies could have informed this submission, for example used in indirect comparisons, or for providing control group data.

Pfizer response:

The systematic review had wider objectives than those specifically required for this submission in order to capture the potential relevant comparators ahead of the NICE scoping meeting. Therefore the inclusion criteria for the review were broader than the scope used for the final submission in order to meet these objectives. The narrower criteria used to include studies within the submission is outline in Table 8 of the company submission. This is in line with the decision problem, which is also included in Table 1 of the company submission.

Summary details of the 4 RCTs included in the SLR, but not included in the submission are presented in Table 2. None of these studies presented any relevant treatments to the NICE decision problem, and they therefore did not allow for any treatment links to be made for inotuzumab compared to other relevant treatments from the NICE scope in order for indirect treatment comparisons to be performed.

Table 1: Summary details of the RCTs excluded from the submission

Study	Population	Intervention(s)	Comparator(s)	Reason for exclusion
NCT01518517	Patients aged 1-55 with Ph- ALL after first relapse	ETY001 (GRASPA®)	L-asparaginase (KIDROLASE)	Not treatments of interest for the NICE decision problem
NCT00123487	Adult patients with Ph+ ALL intolerant or resistant to imatinib	Dasatanib 140mg once daily	Dasatinib 70mg twice daily	Not treatments or comparison of interest to the NICE decision problem
6692	Patients aged 14-66 with acute non-lymphoblastic leukaemia or ALL	Cytarabine + mitoxantrone + quinine	Cytarabine + mitoxantrone	Not treatments or comparison of interest to the NICE decision problem

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TOWER	Adult patients with R/R Ph- B-cell ALL	Blinatumomab	SoC	Blinatumomab is not approved for use by NICE, and is not used in clinical practice and is therefore not a relevant comparator to the NICE decision problem
Key: ALL, acute lymphocytic leukaemia; NICE, National Institute for Health and Care Excellence, Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SoC, standard of care.				

Summary details of the 12 non-RCTs included in the SLR, but not included in the submission are presented in Table 3. These studies either did not present any relevant treatments or any relevant treatment comparisons to the NICE decision problem. Therefore, none of these studies allowed for any treatment links to be made for inotuzumab compared to other relevant treatments from the NICE scope in order for indirect treatment comparisons to be performed.

Table 2: Summary details of the non-RCTs excluded from the submission

Study	Population	Intervention(s)	Reason for exclusion
Faderl et al., 2011	Patients with R/R ALL (including B-cell), previously treated with hyper-CVAD	• Intensified doses of vincristine + dexamethasone + asparginase • Intensified doses of vincristine + dexamethasone + pegaspargase	Not treatments or comparison of interest to the NICE decision problem
Kantarjian et al., 1992	Adult patients with refractory ALL	• High-dose mitoxantrone plus cytosine arabinoside plus GM-CSF • High-dose mitoxantrone plus cytosine arabinoside (historical study)	Not treatments or comparison of interest to the NICE decision problem

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Kantarjian et al., 1989	Adult patients with refractory ALL	• Vincristine + doxorubicin + dexamethasone • Methotrexate + asparaginase • High-dose ara-C • High-dose ara-C + mitoxantrone • L-asparaginase • Cyclophosphamide + carmustine + etoposide + autologous BMT • Cyclophosphamide + etoposide + TBI + allogeneic BMT	Not treatments or comparison of interest to the NICE decision problem
Koller et al., 1997	Adult patients with refractory ALL	• High-dose Ara-C + mitoxantrone with or without GM-CSF • Hyper CVAD	Not treatments or comparison of interest to the NICE decision problem
Weiss et al., 1998	Patients aged 18-60 with R/R ALL or lymphoblastic lymphoma	• Idarubicin 20mg/m^2 with cytarabine • Idarubicin 30mg/m^2 with cytarabine • Idarubicin 40mg/m^2 with cytarabine • Idarubicin 50mg/m^2 with cytarabine	Not treatments or comparison of interest to the NICE decision problem
Yap et al., 1981	Adult patients with ALL who have relapsed on previous chemotherapy	• Asparaginase + ifosafamide + methotrexate • Asparaginase + methotrexate	Not treatments or comparison of interest to the NICE decision problem
Topp et al., 2012	Adult patients with R/R, Ph-, B-cell ALL	Blinotumumab	Blinatumomab is not approved for use by NICE, and is not used in clinical practice and is therefore not a relevant comparator to the NICE decision

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			problem
Lee et al., 2011	Adult patients treated with TKI-based chemotherapy for newly diagnosed Ph+ ALL, who had R/R disease	• HCVAD + imatinib • HCVAD + dasatinib	Not treatments or comparison of interest to the NICE decision problem
Ahn et al., 2015	Adult patients with R/R ALL	• Ara-C + mitoxantrone + etoposide • Ara-C + mitoxantrone	Not treatments or comparison of interest to the NICE decision problem
Pigneux et al., 2011	Adult patients with R/R ALL	• VANDEVOL chemotherapy + dexamethasone • ENDEVOL chemotherapy + cyclophosphamide	Not treatments or comparison of interest to the NICE decision problem
Gokbuget et al., 2011; Gokbuget et al., 2011; Gokbuget et al., 2012	Patients (aged 15-55) with R/R B-cell ALL who relapsed after SCT	• FLAG-IDA • HDAC or HDMTX or VP or VCR or DEXA	Not comparison of interest to the NICE decision problem; patients not currently for second SCT under NHS England, so not relevant population.
Kozlowski et al., 2012	Adult patients (<66 years) with relapsed ALL	• Mitoxantrone, etoposide and cytarabine • Fludarabine, cytarabine, pegylated-asparaginase plus G-CSF • Cytarabine, betamethasone, cyclophosphamide, daunorubicin and vincristine	Not treatments or comparison of interest to the NICE decision problem
Key: ALL, acute lymphocytic leukaemia; Ara-c, cytarabine; BMT, bone marrow transplant; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; DEXA, dexamethasone; FLAG, fludarabine, high-dose cytarabine and G-CSF; G-CSF, granulocyte-colony stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HDMTX, high-dose methotrexate; HIDAC, high-dose intermittent ara-c; IDA, idarubicin; NICE, National Institute for Health and Care Excellence, Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SCT, stem			

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cell transplant; SoC, standard of care; TBI, total body irradiation; TKI, tyrosine kinase inhibitors; VCR, vincristine; VP, vinorelbine, cisplatin.

A6. The eligibility criteria for the systematic review states that studies will not be excluded on the basis of language. However, in the PRISMA diagram (Figure 7 on page 69) two studies were excluded as 'Non-English'. Please explain this inconsistency. In addition, please provide further details for the two studies excluded as 'Not retrieved' – does this mean that full text articles were unavailable?

Pfizer response:

The objective of the SLR was to include studies published in English language only. Therefore a filter for English language studies was applied at the database searching stage. This functionally was available in the Embase database only. However, this still led to the retrieval of a small number of non-English articles in the SLR searches, despite this restriction. As there was no intent to extract any data from non-English studies, they were excluded at the full text screening stage. After consulting two vendors to try and obtain the studies, the two studies that were marked as not retrieved are listed below.

1. Treatment of adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL); Leukemia, 1997; 11 Suppl 4 S28-S30

    - We could not obtain the full text copy of this article. It is a review article but PubMed categorised it as clinical trial and review. We aimed to retrieve the full text article in order to avoid any incorrect exclusion. However, a full text copy was unobtainable

2. Blinatumomab gets complete remissions in relapsed B-ALL; Oncology Report; 2012 :February (16)

    - This was a conference paper. A full text copy was unobtainable.

INO-VATE 1022 trial

A7. **Priority question:** Please check the table below and correct any errors/add missing data that are available. Please also provide the same data for the ITT218 population.

Status	**Inotuzumab (n=164)**	**Standard of Care (n=162)**
Remission outcomes		
Achieved CR	[redacted]	[redacted]

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Achieved CRi	[redacted]	[redacted]
Achieved CR or CRi	[redacted]	[redacted]
MRD negativity in CR/CRi patients	[redacted]	[redacted]
HSCT		
Did not have HSCT	[redacted]	[redacted]
Achieved CR/CRi	[redacted]	[redacted]
Did not achieve CR/CRi	[redacted]	[redacted]
Had HSCT	[redacted]	[redacted]
HSCT and CR/CRi	[redacted]	[redacted]
HSCT but not CR/CRi	[redacted]	[redacted]

Pfizer response:

Table 1 shows the remission outcomes and HSCT data for the ITT patient population as of the 08 March 2016 data cutoff date.

Table 1. INO-VATE 1022: ITT Population (08 March 2016 cutoff date)

Status	Inotuzumab (n=164)	Standard of Care (n=162)
Remission outcomes		
Achieved CR	[redacted]	[redacted]
Achieved CRi	[redacted]	[redacted]
Achieved CR or CRi	[redacted]	[redacted]
MRD negativity in CR/CRi patients	[redacted]	[redacted]
HSCT		
Did not have HSCT	[redacted]	[redacted]
Achieved CR/CRi	[redacted]	[redacted]
Did not achieve CR/CRi	[redacted]	[redacted]
Had HSCT	[redacted]	[redacted]
HSCT and CR/CRi	[redacted]	[redacted]

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Table 1. INO-VATE 1022: ITT Population (08 March 2016 cutoff date)

Status	Inotuzumab (n=164)	Standard of Care (n=162)
HSCT but not CR/CRi	[redacted]	[redacted]

Sources: Study B1931022 sCSR In-text Table 25; Study B1931022 sCSR Table 14.2.2.7.1 (HSCT); Study B1931022 sCSR In-text Table 39 (MRD)

Table 2 shows the remission outcome for the ITT218 patient population as of the 02 October 2014 data cutoff date. In the ITT218 population, the analysis of OS by CR/CRi and SCT was not conducted. This data will be provided to NICE at a later date.

Table 2. INO-VATE 1022: ITT218 Population

Status	Inotuzumab (n=109)	Standard of Care (n=109)
***Remission outcomes* (02 October 2014 cutoff date)**		
Achieved CR, per EAC	[redacted]	[redacted]
Achieved CRi, per EAC	[redacted]	[redacted]
Achieved CR or CRi, per EAC	[redacted]	[redacted]
MRD negativity in CR/CRi (per EAC) patients	[redacted]	[redacted]

Source: Study B1931022 CSR Table 27 (CR/CRi); Study B1931022 CSR Table 39 (MRD)
Abbreviations: CR=complete remission; CRi=complete remission with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplant; ITT218= intent to treat population consisting of the first 218 randomised patients; MRD=minimal residual disease.

In addition to the response sent on 17 March 2017, the Table below shows the HSCT data for the ITT218 patient population as of the 08 March 2016 data cutoff date.

Table 1. Study B1931022: ITT218 Population

Status	Inotuzumab (n=109)	Standard of Care (n=109)
HSCT (08 March 2016 cutoff date)		
Did not have HSCT	[redacted]	[redacted]
Achieved CR/CRi	[redacted]	[redacted]

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Did not achieve CR/CRi	[redacted]	[redacted]
Had HSCT	[redacted]	[redacted]
HSCT and CR/CRi (per EAC)	[redacted]	[redacted]
HSCT but not CR/CRi	[redacted]	[redacted]

Source: Study B1931022 Table 554.A7.14.2.2.7.1.
Abbreviations: CR=complete remission; CRi=complete remission with incomplete hematologic recovery; EAC: Endpoint Adjudication Committee; HSCT=hematopoietic stem cell transplant; ITT218= intent to treat population consisting of the first 218 randomised patients; NE=not estimatable.

SUPPORTING DOCUMENTATION

Study B1931022 CSR Table 27
Study B1931022 CSR Table 39
Study B1931022 sCSR In-textTable 25
Study B1931022 sCSR Table 14.2.2.7.1
Study B1931022 sCSR In-text Table 39

A8. Please provide formal test evidence of non-proportionality in the overall survival data. In addition, please provide further justification for the choice of timepoint in the RMST analysis (37.7 months). Please also provide analyses at other timepoints, e.g. 12 months and 18 months.

Pfizer Response:

[redacted]

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Manchester
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United Kingdom

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Manchester
M1 4BT
United Kingdom

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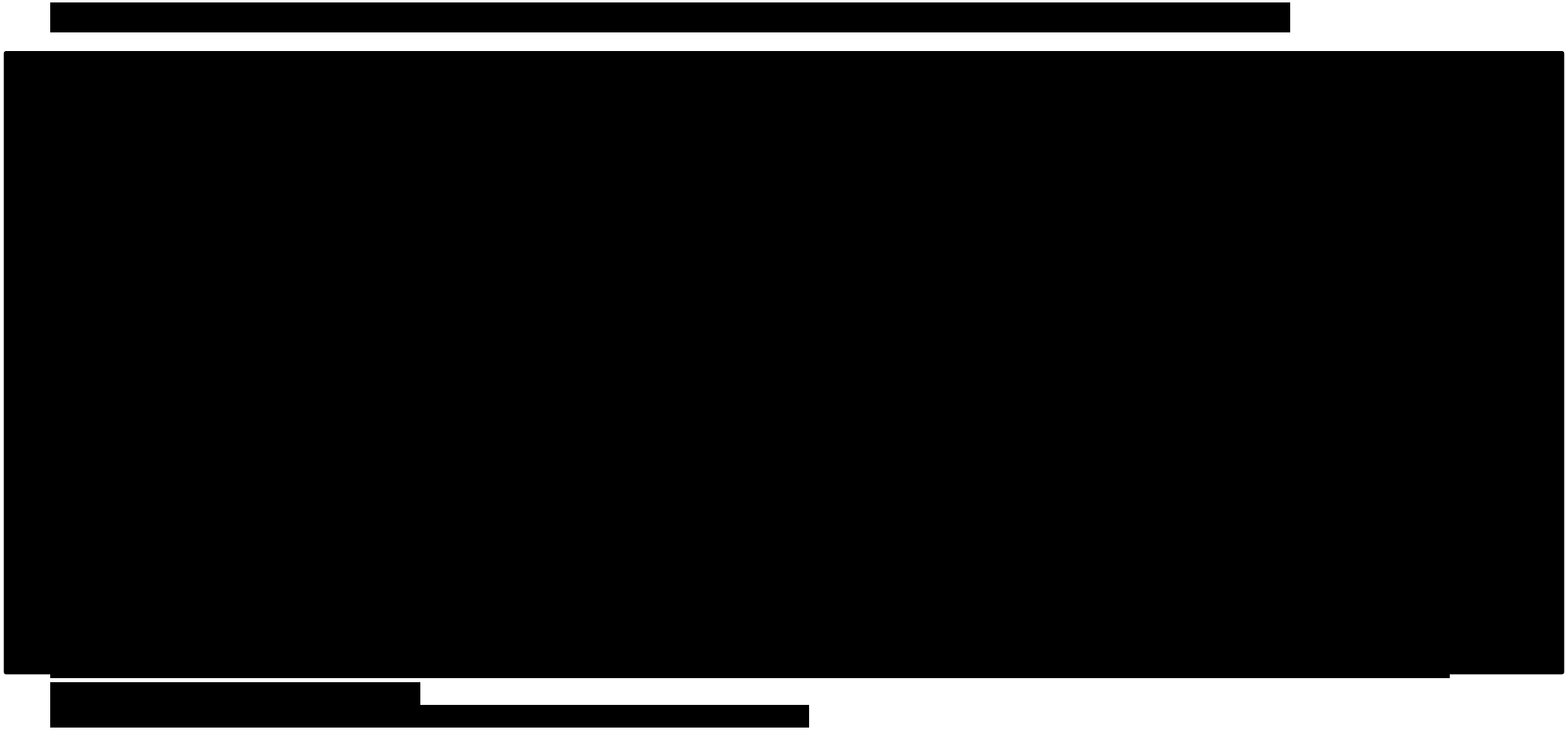
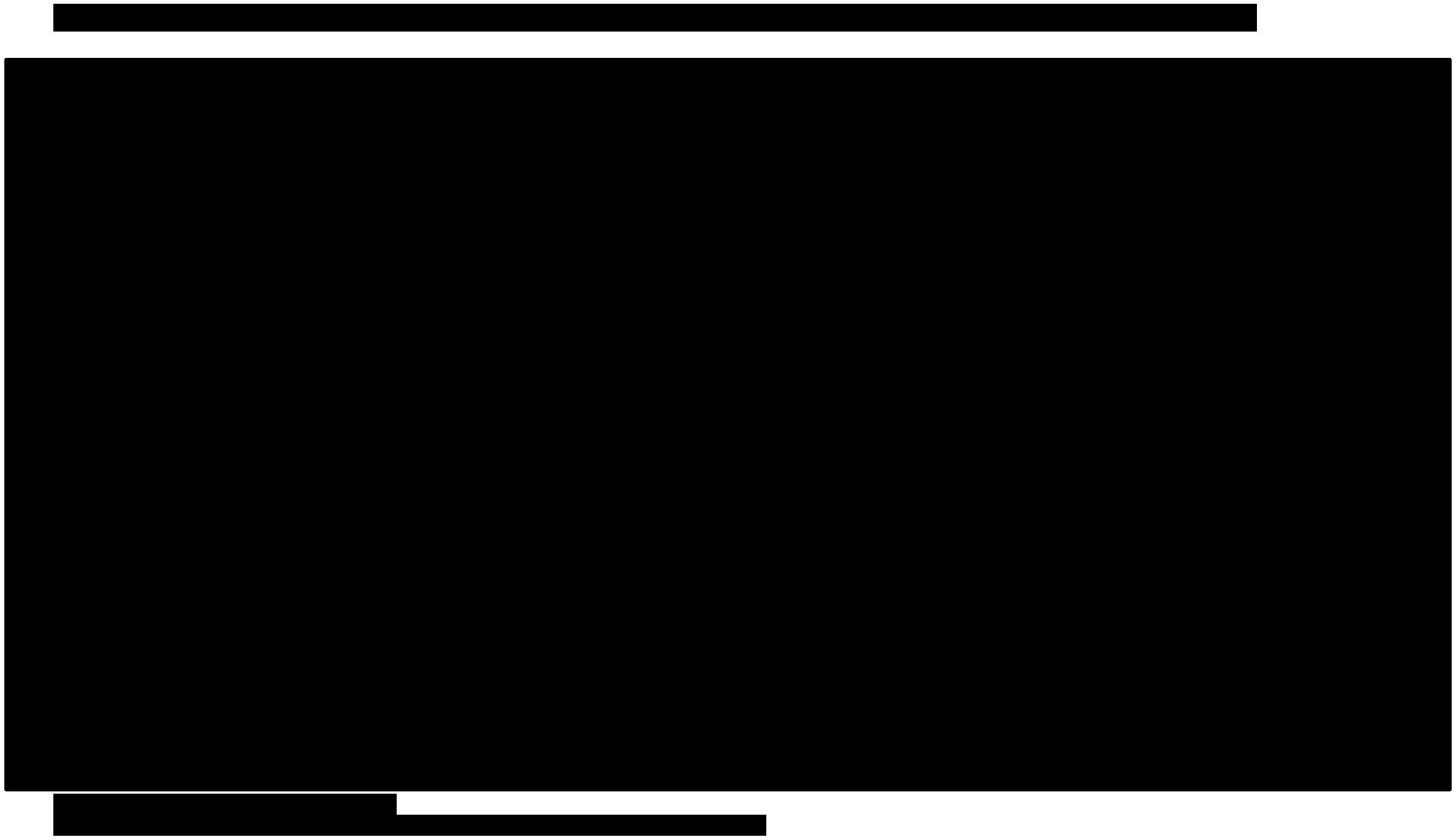
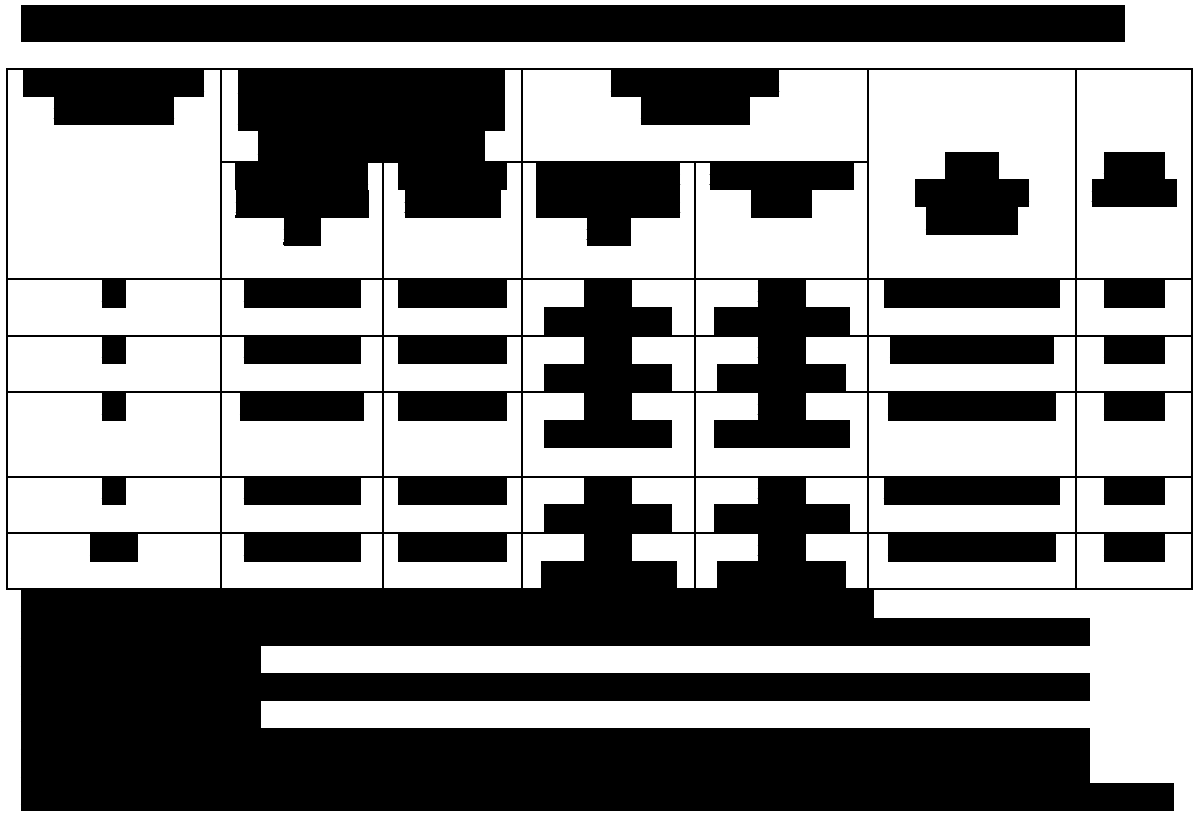




[redacted]



References

None

SUPPORTING DOCUMENTATION

Study B1931022 Table 554.A8.14.2.2.14.1

Study B1931022 Table 14.2.2.14.1

Study B1931022 Figure 554.A8.1

Study B1931022 Figure 554.A8.2

Study B1931022 Figure 554.A8.3

Study B1931022 sCSR, Figure 14.2.2

A9. Please confirm whether patients who received HSCT were removed from the duration of remission (DoR) analyses or censored.

Pfizer response:

No, patients who received HSCT were not removed or censored due to HSCT in the duration of remission (DoR) analyses.

References

None

SUPPORTING DOCUMENTATION

None

A10. Please provide standard 2-sided p-values and 95% CI throughout (where 1-sided p-values and 97.5% CI have been used).

Pfizer response:

Table 1 shows the efficacy results from Study B1931022 presented according to the latest draft of the Summary of Product Characteristics (SmPC) which will be submitted to the European Medicines Agency (EMA) along with responses to the Day 180 questions as part of the Marketing Authorisation Application (MAA) review.

Table 3. Study B1931022: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B cell precursor ALL who received 1 or 2 prior treatment regimens for ALL

	Inotuzumab ozogamicin (N=109)	**HIDAC, FLAG, or MXN/Ara-C (N=109)**
CR[a]/CRi[b]; n (%) [95% CI]	[redacted]	[redacted]

Table 3. Study B1931022: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B cell precursor ALL who received 1 or 2 prior treatment regimens for ALL

	Inotuzumab ozogamicin (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)
CR[a]; n (%) [95% CI]		
CRi[b]; n (%) [95% CI]		
MRD negativity[c] for patients achieving CR/CRi; rate[d] (%) [95% CI]		
Median OS; months [95% CI]		
Median PFS[e]; months [95% CI]		
Median DoR[f]; months [95% CI]		
HSCT rate; n (%) [95% CI]		

Table 3. Study B1931022: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B cell precursor ALL who received 1 or 2 prior treatment regimens for ALL

	Inotuzumab ozogamicin (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)

Sources: Study B1931022, Table 335.14.2.1.1.4 (CR/CRi); Study B1931022, Table 335.14.2.1.5.2 (MRD); Study B1931022, Table 550.14.2.2. (OS); Study B1931022, Table 550.14.2.3.1 (PFS); Study B1931022, Table 530.201.4 (DoR); Study B1931022, Table 335.14.2.7.1 (HSCT).

Abbreviations: ALL=acute lymphoblastic leukaemia; ANC=absolute neutrophil counts; Ara-C=cytarabine; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematological recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HSCT=haematopoietic stem cell transplant; ITT=intent-to-treat; MRD=minimal residual disease; MXN=mitoxantrone; N/n=number of patients; OS=overall survival; PFS=progression-free survival.

[a] CR, per EAC, was defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets $\geq 100 \times 10^9$/L and ANC $\geq 1 \times 10^9$/L) and resolution of any extramedullary disease (Cycle 1 extramedullary disease status).

[b] CRi, per EAC, was defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, partial recovery of peripheral blood counts (platelets $< 100 \times 10^9$/L and/or ANC $< 1 \times 10^9$/L) and resolution of any extramedullary disease (Cycle 1 extramedullary disease status).

[c] MRD negativity was defined by flow cytometry as leukaemic cells comprising $< 1 \times 10^{-4}$ (< 0.01%) of bone marrow nucleated cells.

[d] Rate was defined as number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC.

[e] PFS was defined as the time from date of randomisation to earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi.

[f] Duration of remission was defined as the time since first response of CR[a] or CRi[b] per Investigator's assessment to the date of a PFS event or censoring date if no PFS event was documented. Analysis was based on the ITT population with patients without remission being given a duration of zero and considered an event.

References

None

SUPPORTING DOCUMENTATION

Study B1931022, Table 335.14.2.1.1.4

Study B1931022, Table 335.14.2.1.5.2

Study B1931022, Table 550.14.2.2.

Study B1931022, Table 550.14.2.3.1

Study B1931022, Table 530.201.4

Study B1931022, Table 335.14.2.7.1

A11. **Priority question:** Please provide information on adverse event related deaths.

Pfizer Response:

Study B193022 Grade 5 Adverse Events – All-causality

[redacted]

[redacted] (Study B193022, sCSR Listing 16.2.5.1.1; Study B193022, sCSR Listing 16.2.7).

Study B193022 Grade 5 Adverse Events – Treatment-related

[redacted] (Study B193022, sCSR Table 14.3.1.3.9.1).

Study B193022, sCSR Listing 16.2.7.7),

[redacted] (Study B193022, sCSR Listing 16.2.1.3; Study B193022, sCSR Listing 16.2.7).

Table 4. Study B1931022: All-Causality Grade 5 TEAEs by MedDRA System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Inotuzumab Ozogamicin (N=164) n (%)	Defined Investigator's Choice of Chemotherapy (N=143) n (%)
Any Grade 5 AEs		
General disorders and administration site conditions		
Disease progression		
Multi-organ failure		
Infections and infestations		
Pneumonia		
Sepsis		
Neutropenic sepsis		
Pseudomonal sepsis		
Septic shock		
Klebsiella bacteraemia		
Lung infection		
Pneumonia pseudomonal		
Systemic mycosis		
Hepatobiliary disorders		
Venoocclusive liver disease[a]		
Gastrointestinal disorders		
Colitis ischaemic		
Gastrointestinal haemorrhage		
Intestinal ischaemia		
Intra-abdominal haemorrhage		
Cardiac disorders		
Cardiac arrest		
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome		
Respiratory failure		
Vascular disorders		
Shock haemorrhagic		
Nervous system disorders		
Haemorrhage intracranial		

Source: Study B1931022 sCSR, Table 14.3.1.2.9.1.2.2

Defined Investigator's choice was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).

TEAEs=AEs that commenced on or after C1D1 but within 42 days after the last dose (non-related) or any time after C1D1 (treatment-related). All VOD events within 2 years after randomization date regardless of causal attribution to study therapy were included.

MedDRA (v18.1) coding dictionary was applied. AEs were graded according to the NCI CTCAE, v3.0.

Abbreviations: AE=adverse event; C=cycle; D=day; FLAG=fludarabine, cytarabine, and G-CSF; G-CSF=granulocyte-colony stimulating factor; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; MedDRA=Medical Dictionary for Regulatory Activities; MXN/Ara-C=mitoxantrone and cytarabine; N/n=number of patients; NCI CTCAE=National Cancer Institute common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; v=version; VOD=venoocclusive liver disease.

a. All Grade 5 events of VOD occurred after follow-up allogeneic HSCT.

Table 5. Study B193022: Treatment-Related TEAE Grade 5 Reported in Either Treatment Arm by MedDRA Preferred Term (All Cycles) – Safety Population

Preferred Term	Inotuzumab Ozogamicin (N=164) n (%)	Defined Investigator's Choice of Chemotherapy (N=143) n (%)
Any AEs		
Venoocclusive liver disease		
Acute respiratory distress syndrome		
Intestinal ischaemia		
Multi-organ failure		
Pneumonia		
Septic shock		
Haemorrhage intracranial		
Lung infection		
Respiratory failure		

Source: Study B1931022 sCSR, Table 14.3.1.3.11.1.2.2
Defined Investigator's choice was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
TEAEs=AEs that commenced on or after C1D1 but within 42 days after the last dose (non-related) or any time after C1D1 (treatment-related).
All VOD events within 2 years after randomization date regardless of causal attribution to study therapy were included.
MedDRA (v18.1) coding dictionary is applied. AEs graded according to the NCI CTCAE, v3.0.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; C=cycle; D=day; FLAG=fludarabine, cytarabine, and G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; MedDRA=Medical Dictionary for Regulatory Activities; MXN/Ara-C=mitoxantrone and cytarabine; N/n=number of patients; NCI CTCAE=National Cancer Institute common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; v=version; VOD=venoocclusive liver disease.
a. All 5 cases of VOD/SOS occurred after a follow-up HSCT.

References

None

SUPPORTING DOCUMENTATION

Study B1931022 sCSR, Table 14.3.1.2.9.1.2.2

Study B193022, sCSR Table 14.3.1.3.9.1

Study B1931022 sCSR, Table 14.3.1.3.11.1.2.2

Study B193022, sCSR Listing 16.2.1.3

Study B193022, sCSR Listing 16.2.5.1.1

Study B193022, sCSR Listing 16.2.7

Study B193022, sCSR Listing 16.2.7.7

A12. Please provide further information on the outcomes and characteristics of the 22 patients who had veno-occlusive liver disease (VOD);please clarify which country these patients were from, the number of VOD patients that received dual alkylator conditioning, the number of VOD patients that were aged 55 years or over, and the number of VOD patients who had received prior HSCT.

Pfizer response:

[redacted]

(B1931022 sCSR, Table 14.3.2.3.1):

[redacted]

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[redacted]								
[redacted]								
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[redacted]

[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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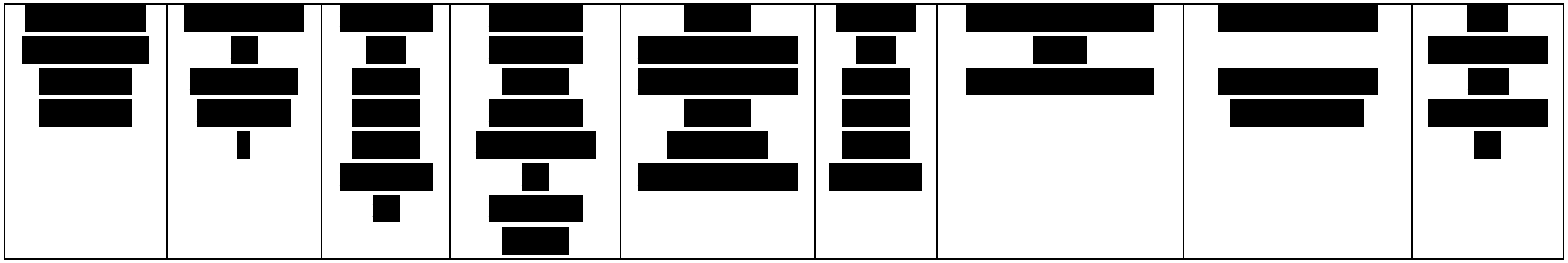

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[redacted]								

Sources for Table 1, Table 2, Table 3, and Table 4: SCS Listing 16.2.7.5.3.200 (B1931022 cases, 08 March 2016 cutoff date), B1931022 sCSR Listing 16.2.5.2.8.2, B1931022 sCSR Listing 16.2.5.1.1

Abbreviations: For race/gender: A=Asian; C=Caucasian; H=Hispanic; B=Black; M=Male; F=Female; ARDS=acute respiratory disease syndrome; ATG=antithymocyte globulin;BU=busulfan; CMV=cytomegalovirus; CY=cyclophosphamide; DUS=disease under study; FLU=fludarabine; GVHD=graft-versus-host disease: GY=Gray; IP = investigational product (ie, inotuzumab ozogamicin); MEL=melphalan; MSD=matched sibling donor; mMRD=mismatch related donor; MUD=matched unrelated donor; mMUD=mismatched unrelated donor; MI=myocardial infarction; MOF=multi-organ failure or multisystem

dysfunction; N/A=notapplicable; RIC=reduced intensity conditioning; RIT=rituximab; SOS=sinusoidal obstruction syndrome; TBI=total body irradiation; THIO=thiotepa; TTP=Thrombotic thrombocytopenic purpura; US=United States; VOD=venooclusive disease.

VOD According to Country

Table 5 shows the occurrence of VOD in patients in Study B1931022 according to country. There were no reports of VOD in the United Kingdom.

Occurrence

Table 5. Study B1931022: VOD/SOS Occurence According to Country

[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Source: B1931022 sCSR Table 14.1.2, SCS Listing 16.2.7.5.3.200 (for B1931022 cases, 08 March 2016 cutoff date)

a. [redacted]

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SUPPORTING DOCUMENTATION

SCS Listing 16.2.7.5.3.200

SCS Table 14.3.1.2.9.2.322

Table 324_14.3.1.7.1.17

B1931022 sCSR Table 14.1.2

B1931022 sCSR, Table 14.3.2.3.1

B1931022 sCSR, Table 14.3.1.2.9.7.1

B1931022 sCSR, Table 14.3.1.7.7.1

B1931022 sCSR Listing 16.2.5.1.1

B1931022 sCSR Listing 16.2.5.2.8.2

B1931022 sCSR, Section 12.3.1.3.1

B1931022 sCSR, Section 12.3.1.3.1.1

B1931022 sCSR, Section 12.3.1.3.1.2

A13. **Priority question:** Please confirm whether the adverse events reported for the safety population (n=143 in standard of care [SoC] arm) for 'all cycles' included adverse events from subsequent medications received (i.e. not just FLAG-based chemotherapy, cytarabine plus mitoxantrone (CM) and high dose cytarabine (HIDAC), as presented in Table 15. Please also provide information on the number of cycles received in the SoC group, and cycle length.

Pfizer response:

[redacted]

References

None

SUPPORTING DOCUMENTATION

Study B1931022 sCSR Table 14.4.1.1.1

Previously Submitted Supporting Documentation

Not applicable

A14. Please provide further information about treatment discontinuations due to study-drug toxicity. In addition, please provide details of dose reductions and temporary discontinuations.

Pfizer response:

[redacted]

References

None

SUPPORTING DOCUMENTATION

Study B1931022 sCSR, Section 12.2.2.1

Study B1931022 sCSR, Section 12.2.2.2

A15. Please provide further information on the reasons why patients dropped out of the trial/withdrew consent prior to receiving treatment in the SoC arm (19 patients), if known. Please also provide baseline characteristics of these 19 patients and details of subsequent medications received. Please confirm whether follow-up data were collected/analysed for these patients. On page 85 of the submission, it states that sensitivity analyses were conducted excluding these patients, with results consistent with the overall analysis. Please provide the results of the sensitivity analyses.

Pfizer response:

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Abbreviations: ECOG: Eastern Cooperative Oncology Group; Ph+: Philadelphia chromosome-positive
Source: Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.1.2.1.2, Table 14.1.2.4.2
a. Ph+ status by central laboratory FISH analysis (BCR ABL ≥7%) or local laboratory results or medical history.
b. The percentages were calculated using the number of patients who received prior regimen #2 as denominator

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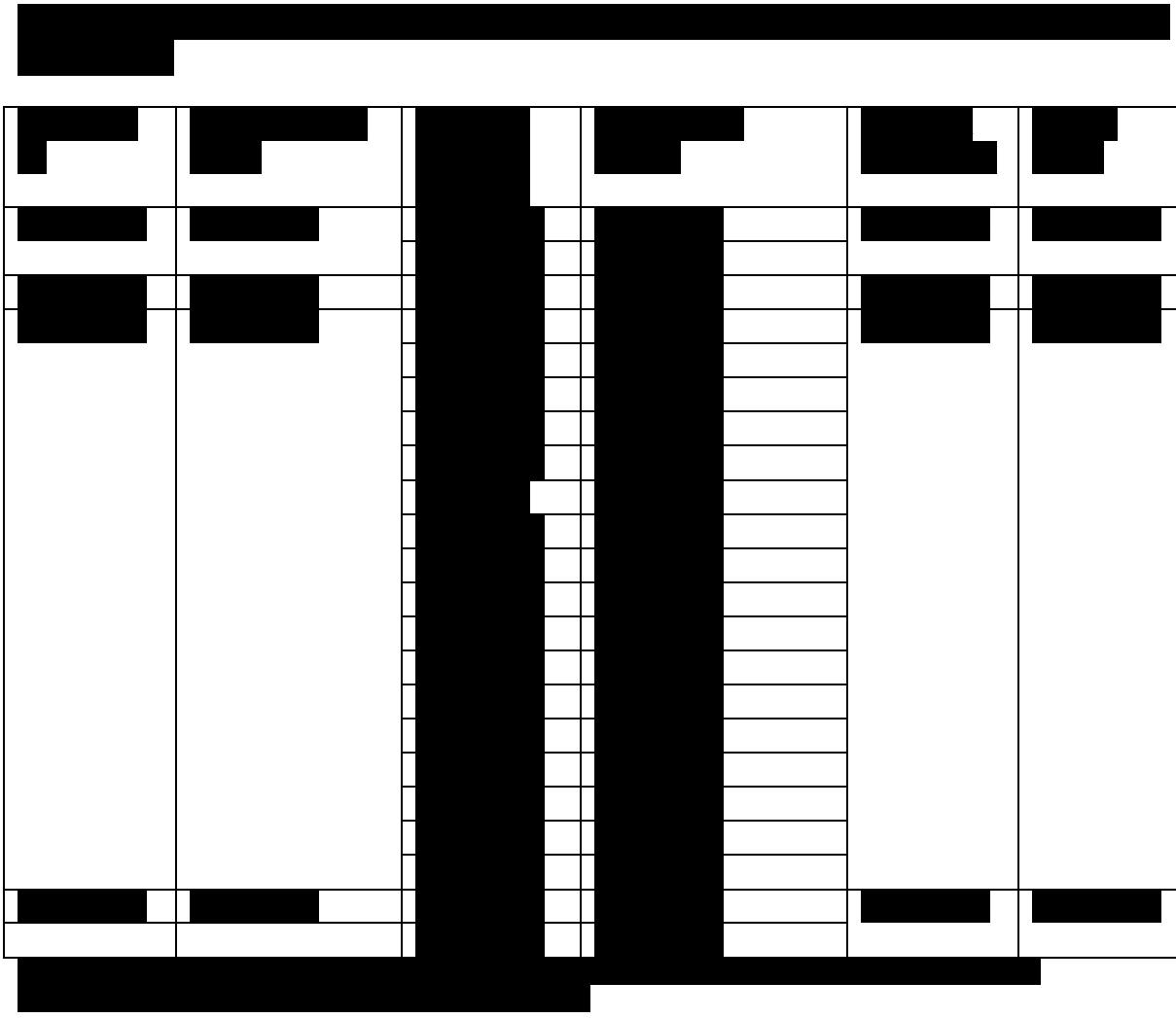

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References

None

SUPPORTING DOCUMENTATION

Module 5, Section 5.3.5.1, Listing 532.16.2.1.9 (new)

Module 5, Section 5.3.5.1, Table 530.193.16 (new)

Module 5, Section 5.3.5.1, Figure 366.14.2.2.15.4 (new)

Module 5, Section 5.3.5.1, Figure 530.193.2 (new)

Module 5, Section 5.3.5.1, Table 530.193.23 (new)

Module 5, Section 5.3.5.1, Figure 530.193.3 (new)

Module 5, Section 5.3.5.1, Study B1931022 sCSR, Table 14.1.1.1

Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.2.2

Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.2.2.1

Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.3.1

Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.2.3.1

Module 5, Section 5.3.5.1, Study B1931022 sCSR Table 14.2.1.1.1.1

A16. **Priority question:** Please provide the reasons why a proportion of patients who achieved complete remission (CR) / complete remission with incomplete haematologic recovery (CRi) did not have HSCT, for both the inotuzumab group and the SoC group.

Pfizer response:

[redacted]

References

None

SUPPORTING DOCUMENTATION

New, Appended, or Replaced Supporting Documentation

Study B1931022, Table 530.202
Study B1931022 sCSR, Table 14.2.4.1.4
Study B1931022 sCSR, Table 14.2.4.2.1
Study B1931022 sCSR, Table 14.2.1.1.1.1

Previously Submitted Supporting Documentation

None

A17. **Priority question:** Please provide justification/further information why 20 patients had HSCT without achieving CR/CRi.

Pfizer Response:

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References

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SUPPORTING DOCUMENTATION

Study B1931022 sCSR, Table 14.2.2.7.1
Study B1931022 sCSR, Listing 16.2.5.2.3
Study B1931022 sCSR, Listing 16.2.5.2.8.2
Study B1931022 sCSR, Listing 16.2.5.2.4
Study B1931022 sCSR, Listing 16.2.6.1.2
Study B1931022 sCSR, Listing 16.2.6.1.8
Study B1931022 sCSR, Listing 16.2.6.1.1
Study B1931022 sCSR, Listing 16.2.1.3
Study B1931022 sCSR, Listing 16.2.8.1.1
Study B1931022 sCSR, Listing 16.2.6.7

A18. Please provide further information about the analyses undertaken for the patient reported outcomes (Table 29 on page 114). If possible, please present the EORTC QLQ-C30 individual scores and EQ-5D and EQ-VAS scores for the inotuzumab group and the SoC group, at the end of each treatment cycle (along with the number of patients who completed the questionnaires in each treatment group at the end of each cycle), along with the change from baseline scores and p-values. In addition, please indicate whether any treatment-time interactions were statistically significant.

Pfizer Response:

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References

None

SUPPORTING DOCUMENTATION

Study B1931022 sCSR, Table 14.2.5.2.1

Study B1931022 sCSR, Table 14.2.6.2.1

Study B1931022 sCSR, Table 14.2.6.3.1

Study B1931022 sCSR, Table 14.2.5.2.2

Study B1931022 sCSR, Table 14.2.6.2.2

Study B1931022 sCSR, Table 14.2.6.3.2

Study B1931022 554.A18.14.2.5.2.1

Study B1931022 554.A18.14.2.6.2.1

Study B1931022 554.A18.14.2.6.3.1

Previously Submitted Supporting Documentation

Company Evidence Submission document (dated February 2017)

A19. The ERG has received clinical advice which considered that patients would receive the first cycle of inotuzumab in an inpatient setting. Please provide data on the number of patients who were treated on an inpatient basis, rather than outpatient basis in the inotuzumab group by treatment cycle. Please discuss the generalisability to clinical practice in England.

Pfizer response:

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Generalisability to clinical practice in England

Based on the clinical expert opinion provided to Pfizer, it is most likely that inotuzumab would be administered in an outpatient care setting, especially as familiarity with the treatment increases. If inpatient stay was required, this would likely be a factor of the disease itself rather that the treatment used.

The issue of inpatient use was discussed at the recent committee meeting for blinatumomab. Although, the same class of treatment, the administration for blinatumomab is continuous and thus more complex over a 28 day cycle compared to inotuzumab, which is only administered [redacted] during a cycle. The clinical experts suggested that for the first cycle of blinatumomab, less than 4 of the 28 days would require inpatient stay. Therefore, as blinatumomab has a more involved administration, Pfizer believes that in comparison, this reinforces our recommendation that inpatient stay would not be required for inotuzumab.

A20. Table 9 on page 39 of the Appendices presents subgroup data suggesting better OS results for patients from North America. Table 11 on page 40 presents subgroup data, suggesting that progression free survival results may be better for patients from the European Union. Please provide further details to allow the ERG to assess these differences, e.g. did different regions use different comparators, different rates of HSCT, different population characteristics?

Pfizer response:

[redacted]

A21. Please confirm whether the full ITT population, in addition to the ITT218 population (the first 218 randomised patients), had CR/CRi assessments reviewed by an independent Endpoint Adjudication Committee.

Pfizer Response:

[redacted]

[redacted]

[redacted]

References

None

SUPPORTING DOCUMENTATION

Study B1931022 CSR Table 14.2.1.1.4

Study B1931022 sCSR Table 14.2.1.1.1

Previously Submitted Supporting Documentation

Not applicable

Non-randomised evidence

A22. **Priority question**: Please provide baseline characteristics for patients included in the non-RCT studies.

Pfizer response:

The major baseline characteristics for the non-randomised trials, Pfizer-sponsored Phase 1/2 Study B1931010 and an Investigator-initiated research (IIR) Phase 2 study conducted at the MD Anderson Cancer Center (MDACC; Houston, Texas, US), are shown in Table 1 below.

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Manchester
M1 4BT
United Kingdom

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Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

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References

Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer 2013;119(15):2728-36.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival and overall survival for the following:

Pfizer response:

The KM figures presented below (Figures 3, 5,7,8,9 and 11) are those presented within the cost-effectiveness section of the submission (Section 5.3) and correspond to the safety population. These data are used to inform the model base case. All other curves are provided as requested but have not been explored within the current cost-effectiveness analysis. Please note that for OS and PFS, the results from the safety population are consistent with the results in the ITT population.

(i) Figures 8 (page 95) and 9 (page 98) are reported for the ITT population. Please provide similar figures for the safety population.

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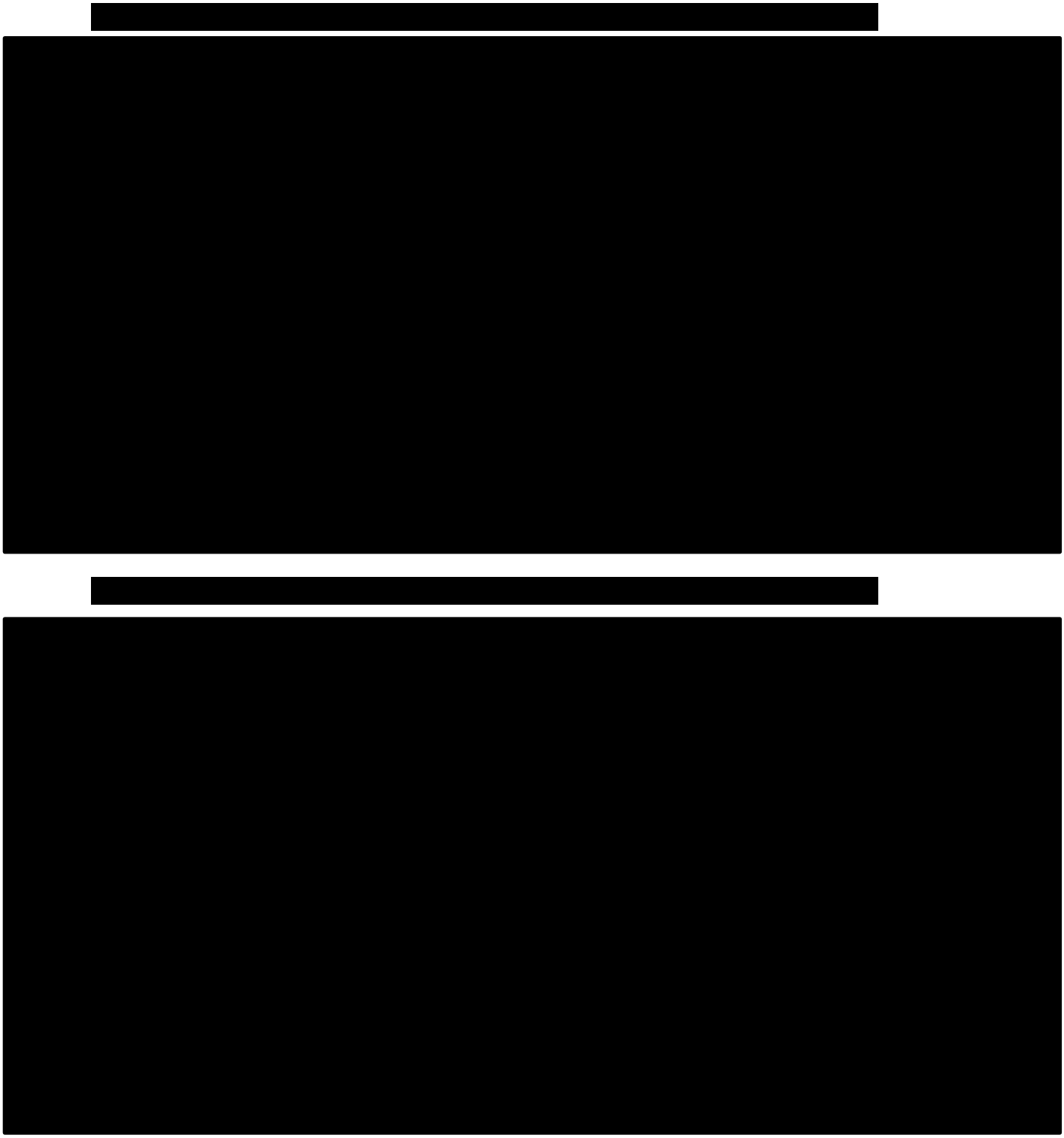
(ii) Figure 26 (page 174) – please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.



(iii) Figure 27 (page 175) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

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(iv) Figure 32 (page 179) – please provide an additional figure including number of patients at risk at each time point.

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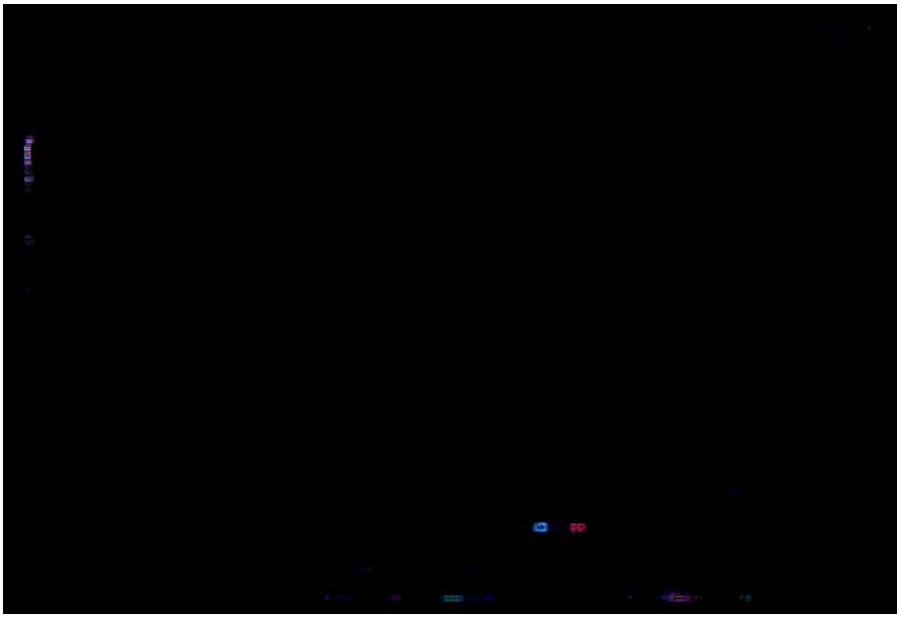
(v) Figure 33 (page 180) – please provide an additional figure including number of patients at risk at each time point.

[redacted]

(vi) Figure 38 (page 187) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

Please note the populations included in the ITT and safety KMs for PFS post SCT are identical, this is due to the one untreated patient in the SCT group already having been removed as the PFS record for this patient occurred prior to SCT

[redacted]



[redacted]

(vii) Figure 39 (page 187) - please provide an additional figure including number of patients at risk at each time point and a similar figure for the ITT population.

[redacted]

[redacted]

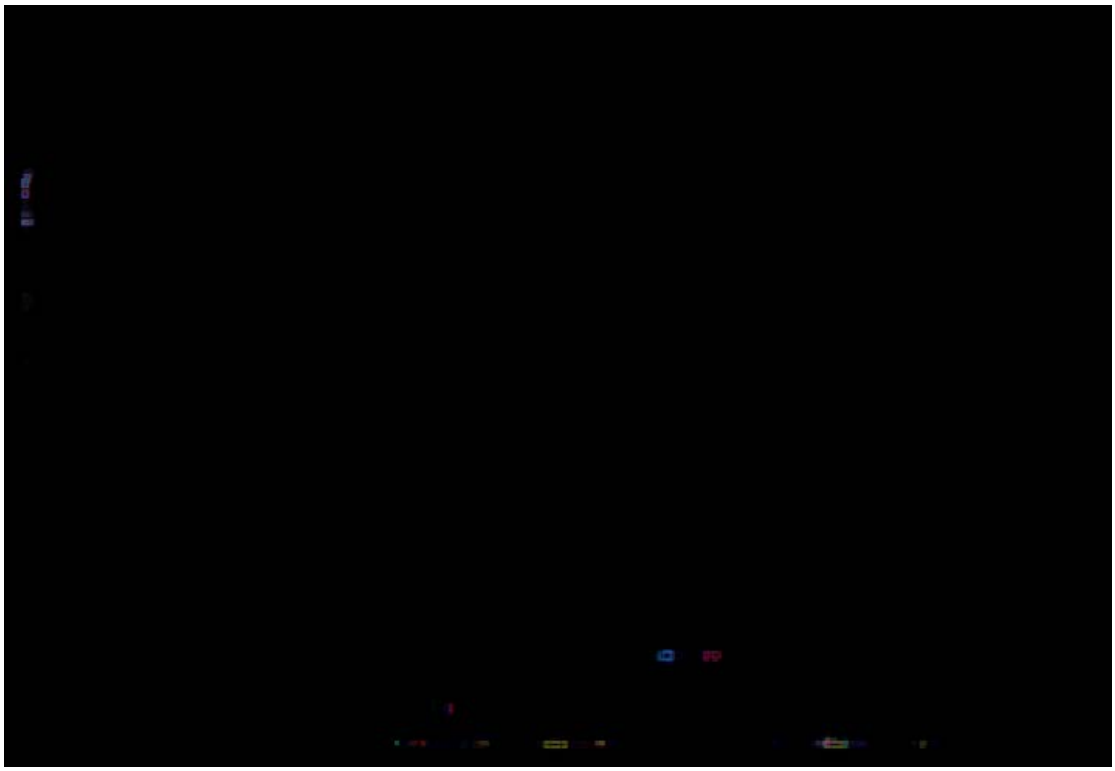
B2. **Priority question**: Please provide additional Kaplan-Meier curves comparing inotuzumab and SoC (<u>with the number of patients at risk at each time point</u>) for progression free survival and overall survival in post-HSCT-patients. Specifically, please provide separate figures for: (i) CR/CRi & post-HSCT patients and (ii) no CR/CRi & post-HSCT patients. Please provide the figures for the safety and ITT population.

Pfizer response:

As above, the populations included in the ITT and safety KMs for PFS post SCT are identical. This is due to the one untreated patient in the SCT group already having been removed as the PFS record for this patient occurred prior to SCT. Due to the definition of PFS, ‘no CR/CRi & post-HSCT’ patients are taken to have an event at SCT date, which leads to the drop shown in Figure 14 and Figure 16 below.

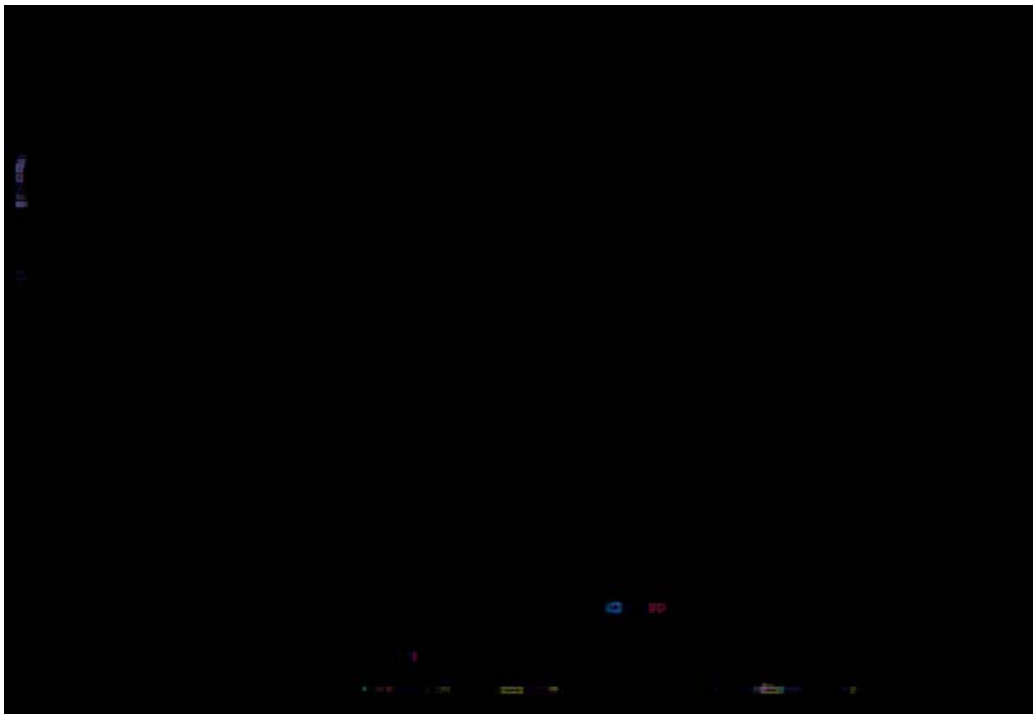
[redacted]

[redacted]



[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

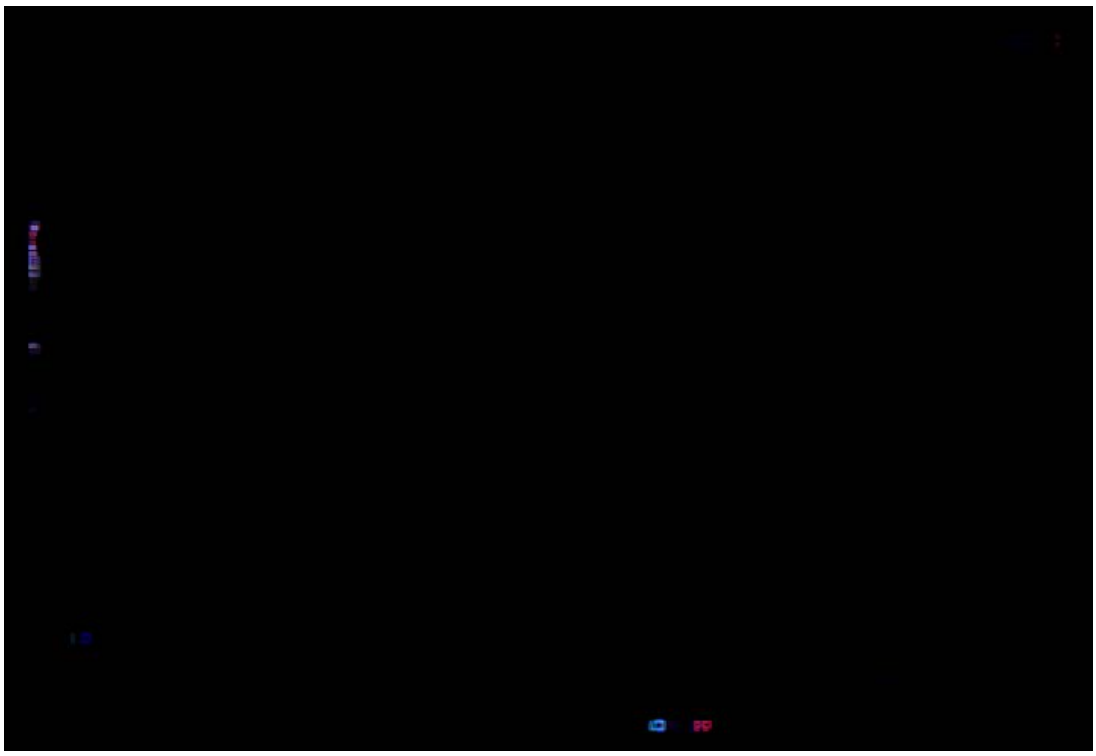
[redacted]

B3. **Priority question**: Please present additional Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival and overall survival for all post-HSCT patients (i.e. pooling the inotuzumab and SOC patients). Please provide the figures for the safety and ITT population.

Pfizer response:

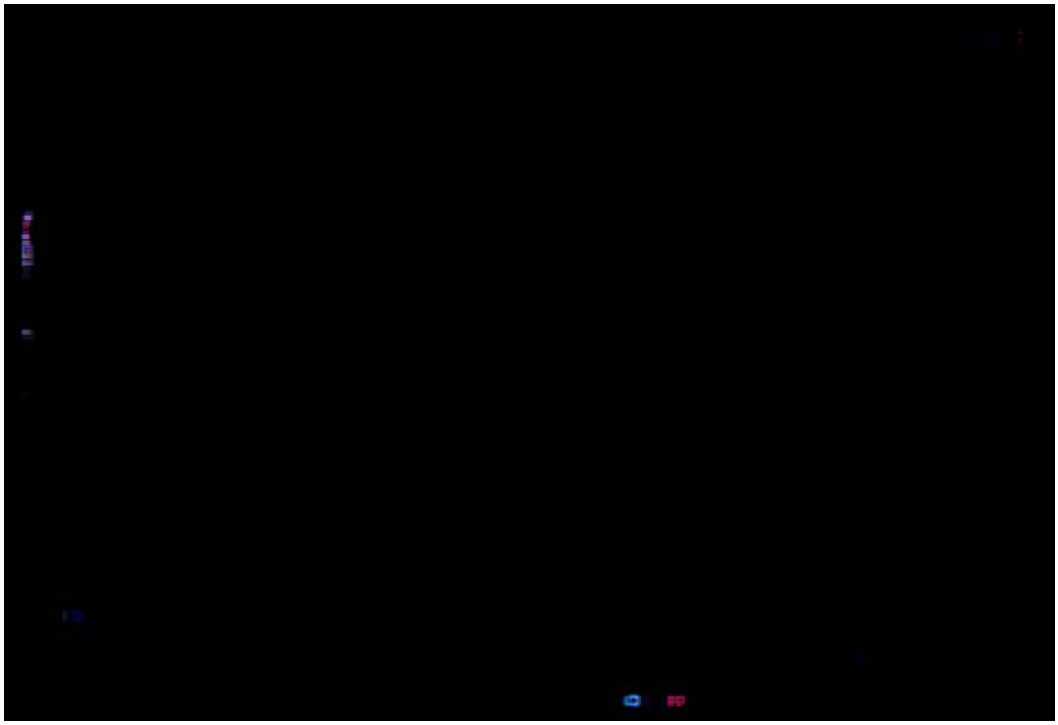
As above, the populations included in the ITT and safety KMs for PFS post SCT are identical. This is due to the one untreated patient in the SCT group already having been removed as the PFS record for this patient occurred prior to SCT.

[redacted]



[redacted]

[redacted]



[redacted]

Although pooling the data creates a larger evidence which can be used to inform post-HSCT survival, doing so fails to account for prognostic factors associated with overall survival that may differ by treatment, for example MRD negativity. Therefore pooling survival post-transplant should be interpreted with extreme caution as we believe that they are neither appropriate nor clinically plausible and will lead to an extremely biased estimate of cost effectiveness. Further explanation on this point can be found in the response to question B4.

B4. **Priority question**: Please incorporate additional functionality in the Excel model to incorporate the requested pooled post-HSCT patient analysis (clarification point B3) and present results for a separate scenario in the cost-effectiveness analyses based on this – including deterministic and probabilistic estimates assuming: (i) 3.5% discount rate for costs and outcomes and (ii) 1.5% discount rate for costs and outcomes.

Pfizer response:

Table 6 to Table 9 report the deterministic and probabilistic results of the pooled post-HSCT data for the safety population applying discount rates of 1.5% and 3.5%. The results when considering the ITT population is reported in Tables 10 to Table 13.

Pooling the data fails to account for prognostic factors associated with overall survival that may differ by treatment. Furthermore, pooling also abandons the available randomised, controlled evidence past the point of transplantation.

A key prognostic factor in *de novo* ALL, which we believe can be extrapolated in R/R disease is MRD negativity. MRD status has been explored within the literature and is considered an important prognostic factor in ALL which is associated with better overall survival outcomes [1-5]. MRD status was also considered as one of the most important prognostic factors associated with survival by UK leading clinicians in ALL at a recent advisory board [6]. Furthermore, when exploring the survival of MRD negative patients compared to MRD positive patients from the INO-VATE-1022 study, there is a clear benefit in survival. Within the INO-VATE-1022 study significantly more patients within the inotuzumab arm achieved MRD negativity compared to those within the SoC arm (76.4% versus 32.1%) (see Figure 11 and 12 within the appendices of the company submission).

Given its importance in determining survival, this should be considered within the analysis. Within the company submission a scenario is provided that pools the post-HSCT data for PFS and OS with a covariate adjustment for MRD negativity. If a pooled dataset is considered, this estimate is a more valid approach than dismissing the impact of MRD negativity. However, even this approach is a departure from the base case which is the most appropriate use of the randomised controlled evidence available. This uses the entire dataset for the safety population and the only covariate that differs is the proportion of patients in the post-HSCT health state that achieved MRD negativity. This results in an ICER of £56,819/QALY. This can be seen within Table 83 within the company submission.

Based on the rationale above, the ICERs should be interpreted with extreme caution as they are neither appropriate nor clinically plausible and will lead to an extremely biased estimate of cost effectiveness.

Table 10: Scenario analysis using pooled post-HSCT in both treatment arms (safety) – deterministic (1.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£85,512
SoC	£64,616	1.20	2.93				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 11: Scenario analysis using pooled post-HSCT in both treatment arms (safety) – probabilistic (1.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£87,854
SoC	£64,406	1.24	3.32				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 12: Scenario analysis using pooled post-HSCT in both treatment arms (safety) – deterministic (3.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,360
SoC	£64,000	0.94	2.93				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 13: Scenario analysis using pooled post-HSCT in both treatment arms (safety) – probabilistic (3.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£117,091
SoC	£63,850	0.98	3.35				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 14: Scenario analysis using pooled post-HSCT in both treatment arms (ITT) – deterministic (1.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,114
SoC	£62,625	1.11	2.73				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 15: Scenario analysis using pooled post-HSCT in both treatment arms (ITT) – probabilistic (1.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,676
SoC	£62,681	1.18	3.19				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care

Table 16: Scenario analysis using pooled post-HSCT in both treatment arms (ITT) – deterministic (3.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£109,364
SoC	£62,053	0.88	2.73				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC,

	Costs	QALYs	LYs	Incremental	ICER
standard of care					

Table 17: Scenario analysis using pooled post-HSCT in both treatment arms (ITT) – probabilistic (3.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£109,951
SoC	£62,036	0.93	3.17				
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care							

References

1. Hoelzer D. Personalized medicine in adult acute lymphoblastic leukemia. *Haematologica*. 2015; 100(7):855-8.
2. Ribera JM, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. *Journal of Clinical Oncology*. 2014; 32(15):1595-604.
3. Jabbour E, Short NJ, Jorgensen JL, et al. Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Cancer*. 2017; 123(2):294-302.
4. Hettle RC, M. Hinde, S. Hodgson, R. Jones-Diette, J. Woolacott, N. Palmer, S. . Exploring the assessment and appraisal of regenerative medicines and cell therapy products. 2015 (Updated: December 2015). Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/final-york-report-march-16.pdf Accessed: 21 November 2016.
5. Nagafuji K, Miyamoto T, Eto T, et al. Monitoring of minimal residual disease (MRD) is useful to predict prognosis of adult patients with Ph-negative ALL: results of a prospective study (ALL MRD2002 Study). *Journal of Hematology & Oncology*. 2013; 6:14.
6. Pfizer Inc. Advisory Board in R/R B-Cell ALL. 17 November. Data on File.

B5. **Priority question**: The methods used to deal with non-proportional hazards do not appear conventional and also appear potentially inconsistent (i.e. shape and scale parameters are not modelled the same way). Please provide further justification for this approach and the appropriateness of this method compared to more conventional alternatives (e.g. independent functions) or utilising as much as the Kaplan-Meier data as possible.

Pfizer response:

The parametric curve methods used for modelling OS and PFS for each of the three patient groups (No CR/CRi & no HSCT, CR/CRi & no HSCT and SCT & Post-HSCT) are more flexible than standard models which typically include one treatment effect (i.e., models that assume proportional hazards or constant treatment effect for

the accelerated failure time model distributions). The additional flexibility of model fits in our analyses comes from the fact that treatment can affect two distributional parameters rather than one (e.g., for Weibull, this would be shape and scale rather than just scale). The models, however, cannot be characterised as “fully-stratified”, as they not rely on separate datasets by treatment group.

By allowing treatment to affect two parameters, this enables a form of stratification by treatment, while maintaining a common effect for the remaining covariates in the model. Although this does require an assumption of proportionality for each covariate, it importantly allows the effect of these covariates to be consistent, regardless of treatment group. This is clinically appealing, as well as technically important, because we must properly control for the fact that the analyses split by the three patient groups are no longer a strictly randomised comparison.

These models were fit using R, specifically the ‘flexsurv’ package (Jackson 2016). The guidance for ‘flexsurv’ gives an example for the case of a generalised gamma curve, which allows an ancillary parameter (such as ‘shape’) to depend on the treatment covariate, providing ‘a model with a time-dependent effect that is neither proportional hazards (PH) nor accelerated failure time (AFT)’ (Jackson 2016).

In comparison to the current approach of partial stratification, fitting fully stratified models for each treatment reduces sample size, and can lead to convergence issues, due to the splitting of the data into the various patient groups. By way of example, fitting curves to post-SCT PFS would lead to curves fitted to a set of [redacted]

As requested, differences between model fits were investigated for: fully stratified curves; curves where all covariates inform 2 distributional parameters (e.g. shape and scale for Weibull); and curves (as are used within the model) which are partially stratified (that is, in which only the treatment covariate affects the two parameters). Both additional types of model have been fitted to the curves chosen as the base case for OS and PFS; from these, AIC and BIC values were compared for each patient group.

The results of these comparisons (Table 1 and Table 2) show that the method we have selected provides statistically better model fits (via AIC and BIC) compared to these two alternative methods in all but one instance (with the exception being the HSCT group for PFS, for which data are scarce.). This provides additional support for the choice of parametric survival modelling within the submission.

Reference:

Christopher Jackson (2016). flexsurv: A Platform for Parametric Survival Modeling in R. Journal of Statistical Software, 70(8),1-33. doi:10.18637/jss.v070.i08

Table 18: AIC and BIC values for base case models comparing fully stratified and partially stratified curves: OS

Outcome: OS	Base case curve	**Parametric curves - treatment effect on two distributional parameters (partially stratified)**		Full stratified parametric curves		Parametric curves – all covariates inform two distributional parameters	
Group		AIC	BIC	AIC	BIC	AIC	BIC
No CR/CRi & no HSCT	Log-logistic	1308.98	1342.23	1313.77	1353.68	1313.85	1369.26
CR/CRi & no HSCT	Log-logistic	892.24	920.82	898.71	931.70	892.99	940.63
HSCT & Post-HSCT	Gompertz	947.05	979.35	946.64	983.27	947.76	1001.59

Table 219: AIC and BIC values for base case models comparing fully stratified and partially stratified curves: PFS

Outcome: PFS	Base case curve	**Parametric curves - treatment effect on two distributional parameters (partially stratified)**		Full stratified parametric curves		Parametric curves – all covariates inform two distributional parameters	
Group		AIC	BIC	AIC	BIC	AIC	BIC
No CR/CRi & no HSCT	Log-logistic	1031.88	1065.13	1039.87	1079.77	1039.78	1095.19
CR/CRi & no HSCT	Log-normal	827.74	856.32	834.44	867.43	841.69	889.33
HSCT & Post-HSCT	Gompertz	651.75	679.24	639.33	664.80	657.10	702.91

B6. **Priority question**: Please present additional analyses to further support the appropriateness and validity of this of this approach (relating to query B5), including:

(i) Please present estimates of restricted mean survival time (RMST) for progression free survival and overall survival for each of the 3 subpopulations (No CR/CRi, CR/CRi and no HSCT and Post HSCT) based on the following time points: 12, 18, 24 and 36 months.

Pfizer Response:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 20. [redacted]

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=[redacted])			Investigator's Choice (Control) (n=[redacted])			Difference in RMST (InO – Control)	
[redacted]								
[redacted]								
[redacted]								

Source: Study B1931022, Table 554.B6.14.2.2.14.6

[a] If the minimum of maximum PFS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

[redacted]

[redacted]

[redacted]

[redacted]

Table 21 [redacted]

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=[redacted])			Investigator's Choice (Control) (n=[redacted])			Difference in RMST (InO – Control)	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]							

Source: Study B1931022, Table 554.B6.14.2.2.14.8

* If the minimum of maximum PFS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

[redacted]

[redacted]

[redacted]

Table 22 [redacted]

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=[redacted])			Investigator's Choice (Control) (n=[redacted])			Difference in RMST (InO – Control)	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	

Source: Study B1931022, Table 554.B6.14.2.2.14.7

[a] If the minimum of maximum PFS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

RMST Analyses for Overall Survival (OS)

Table 23:

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=)			Investigator's Choice (Control) (n=)			Difference in RMST (InO – Control)	

								[redacted]	

Source: Study B1931022, Table 554.B6.14.2.2.14.3

[a] If the minimum of maximum OS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

[redacted]

Table 24 Study B1931022: RMST Analyses (Under Various Truncation Time) for OS for Patients who Achieved CR/CRi Without Follow-Up HSCT– ITT Population

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=[redacted])			Investigator's Choice (Control) (n=[redacted])			Difference in RMST (InO – Control)	
	[redacted]							
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Source: Study B1931022, Table 554.B6.14.2.2.14.5

[a] If the minimum of maximum OS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

[redacted]

Table 25 [redacted]

Truncation Time Tau, months; planned (actual [a])	Inotuzumab ozogamicin (InO) (n=[redacted])			Investigator's Choice (Control) (n=[redacted])			Difference in RMST (InO – Control)	
[redacted]								

Source: Module 5, Section 5.3.5.1, Table 554.B6.14.2.2.14.4

[a] If the minimum of maximum OS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

[redacted]

[redacted]

References

- Trinquart L, Jacot J, Conner SC, and Porcher R. Comparison of Treatment Effects Measured by the Hazard Ratio and by the Ratio of Restricted Mean Survival Times in Oncology Randomized Controlled Trials. Journal of Clinical Oncology 2016, 34:1-8.

SUPPORTING DOCUMENTATION

- Study B1931022, Table 554.B6.14.2.2.14.3
- Study B1931022, Table 554.B6.14.2.2.14.4
- Study B1931022, Table 554.B6.14.2.2.14.5
- Study B1931022, Table 554.B6.14.2.2.14.6
- Study B1931022, Table 554.B6.14.2.2.14.7
- Study B1931022, Table 554.B6.14.2.2.14.8

(ii) Please provide further evidence to support the appropriateness of including a treatment effect on the shape parameter in the selected regressions (e.g. provide formal tests such as testing for a constant time ratio or proportional odds).

Pfizer response:

Pfizer response:

Please refer to the response to question B5. Further analyses to support the appropriateness of including a treatment effect on the shape parameter within the parametric survival model are discussed in B5.

(iii) Please provide further justification for only including treatment as a covariate (but not other covariates) on the shape parameter.

Pfizer response:

Please refer to the response to question B5. Further analyses to support the appropriateness of including a treatment effect on the shape parameter within the parametric survival model are discussed in B5.

B7. **Priority Question:** Please provide additional clinical evidence to support the "cure point" of 3-years used in the model and the assumptions employed beyond this time point.

(i) Several clinical studies have reported lower long-term survival after allogenic HSCT (e.g. Wingard et al, Journal of Clinical Oncology, 2011; Bhatia et al, Blood, 2007) compared to the general population. Please discuss the generalisability of these studies and any implications for the current assumptions in the company model.

Pfizer response

Cure points have previously been used (stated in section 5.3.5 of the company submission) to characterise the point at which patients revert to the mortality of the normal population rate. Based on clinical expert opinion, a cure point between 2 – 5 years is plausible. In the base case, a cure point of 3 years was chosen following clinical expert consultation. To explore the impact of the different cure points, scenario analyses from the cure point range were applied (Table 83 of the company submission), across which the ICERs remained below the willingness to pay threshold of £50,000/QALY.

The model still considers the impact of HRQoL after the cure point in an attempt to reflect clinical reality. Utility values from the literature (Aristides et al, 2015)

were applied to reflect lower HRQoL scores compared to the normal population. This was done to capture potentially reduced quality of life as a result of comorbidities. Furthermore, progression was still possible in the model; which resulted in a further reduction in utility. This is a more conservative approach than the utilities from either the blinatumomab SMC submission (SMC Drug ID: 1145/16) or other literature (Kurosawa et al, 2016), both of which reduced the deterministic ICER to between £29,865 and 35,660/QALY (see Table 82-83 of company submission).

In terms of generalisability, management of patients is improving year on year as suggested by the mortality rate by transplantation year in Bhatia et al and Wingard et al. Although the studies cited in the question suggest slightly lower mortality rates post cure point, these studies were conducted with cohorts of patients treated from 1974 - 2003 and likely overestimate the mortality rates seen in current clinical practice in 2017.

Bhatia et al, also showed that mortality is concentrated in the first years post-transplant (i.e. before the cure point). This demonstrates two points: (i) the risk of mortality dramatically decreases post this cure point and (ii) the use of their relative risk will lead to double counting as the INO-VATE 1022 trial survival data is used to consider the increased risk of mortality in the initial years post-transplant.

(ii) Please clarify whether evidence of longer term mortality following HSCT was systematically considered within any of the reviews in the company submission.

Pfizer response:

Within the SLR, both overall survival and mortality were included as outcomes of interest. Where long term outcomes were reported, these were captured if the study had met the inclusion criteria. However, the reviews were specific to the decision problem and did not include a search solely focussing on post-HSCT longer term mortality.

(iii) Please incorporate additional flexibility in the Excel model to allow a higher standardised mortality ratio to be applied in the post-cure period compared to the general population. Please provide additional scenarios for the cost-effectiveness results based on assuming higher standardised mortality ratio rates and with reference to existing clinical literature.

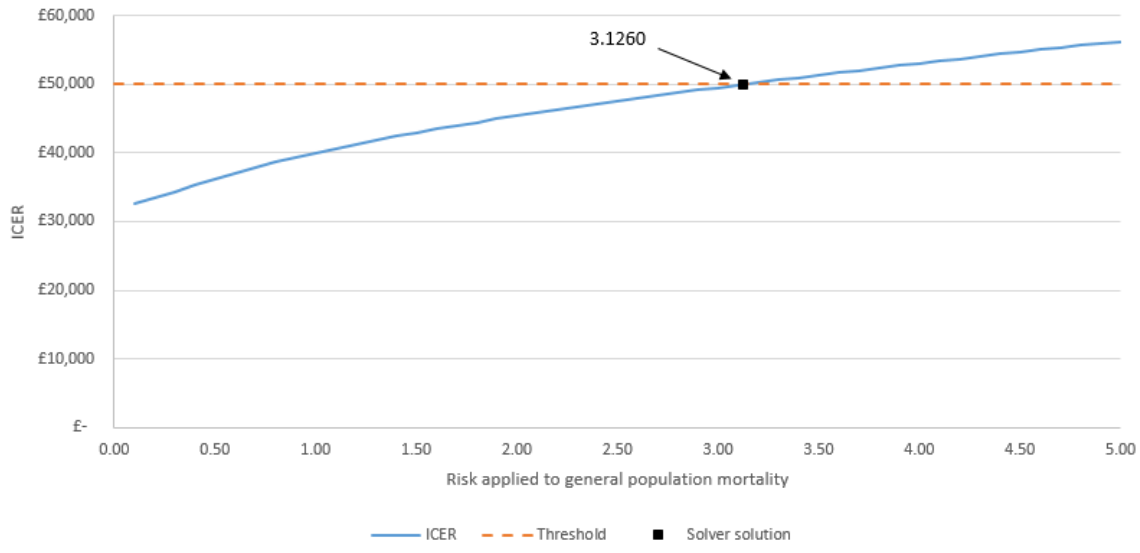
Pfizer response:

The functionality of applying a higher standardised mortality ratio to the general population has been incorporated into the model and is included with our response.

Studies identified within the SLR were searched for post-HSCT specific OS. No studies were identified that were relevant to the decision problem that reported OS from the point of transplant, which could be used to derive a higher standardised mortality rate. The two studies identified by the ERG in question B7 (i) (Wingard et al 2011 and Bhatia et al, 2007) found "excellent" longer term survival post-HSCT, particularly past the "cure" point used in our model. As stated in the response above, we expect the rates of survival to be even higher, suggesting that any plausible adjustment to the mortality rate should be minimal.

To explore the point at which an adjustment to the longer term mortality would impact the cost-effectiveness of inotuzumab, a threshold analysis is presented below. This analysis explores the maximum rate ratio at which inotuzumab would remain cost effective at a willingness-to-pay threshold of £50,000 per QALY. The results of this analysis are presented in Figure 25 below. Excel solver was run to find this risk. The excel solution resulted in a relative risk of 3.126 (3.d.p), indicating that patients that have undergone HSCT and survived to a cure point of 3 years, would have 3.126 times the risk of death compared to the general population. This value seems very large given the curative intent of HSCT. By definition, the purpose of the cure point means that the probability of relapse after the cure point is rare. In the non-relapse, post-HSCT population Bhatia et al estimates the increased relative risk of mortality is 0.2, This suggests that there is no difference to the mortality rate post HSCT.

Figure 1: Threshold analysis on relative risk applied to general population mortality



B8. Please provide further justification for incorporating additional costs but no additional benefits for: (i) FLAG-IDA (fludarabine, cytarabine and granulocyte-colony stimulating factor plus idarubicin) vs FLAG alone; (ii) TKI (imatinib) – in patients with Ph+

disease only. Present an additional scenario analysis assuming the costs of FLAG alone and excluding TKI costs.

Pfizer response:

Adding TKIs:

Due to the paucity of comparative evidence, it is difficult to estimate the additional benefit attributable to adding a TKI in terms of efficacy in Ph+ patients. In the absence of efficacy data, the model reflects what the NHS pays for this treatment regimen. When the cost of adding a TKI is removed, this has no effect on inotuzumab's cost effectiveness with an ICER of £40,615/QALY (approximately £600 higher than the base case of £40,013/QALY).

It is important to note that recently approved TKIs, such as dasatinib and ponatinib, are more costly than established TKIs such as imatinib. Therefore, a conservative approach was applied with regards to cost in the model (only the cost of imatinib was used).

Adding IDA:

Although the additional benefit was not captured, given the additional toxicity of IDA, it is assumed that any additional benefit would be offset by the toxicity, as stated by the clinical experts at the advisory board [1]. To understand the impact of using the cost of IDA on the ICER, the additional scenario analysis shows that this has no effect on inotuzumab's cost effectiveness with an ICER of £40,419/QALY (approximately £300 higher than the base case of £40,013/QALY).

Reference

[1] Pfizer Inc. Advisory Board in R/R B-Cell ALL. 17 November. Data on File.

B9. The acquisition cost and funding status of several therapies assumed for subsequent induction treatments appears uncertain. Please present an additional scenario analysis assuming where the costs applied for patients receiving blinatumomab and inotuzumab are replaced with the costs of chemotherapy.

Pfizer response:

Within the INO-VATE-1022 trial, subsequent induction therapy was administered to patients which may have impacted OS. Given the model uses OS observed within the trial, the inclusion of the costs associated with these treatments in the economic model seems appropriate to minimise any bias. Treatments considered within the economic analysis were those which would be considered relevant and available in a UK setting, either through reimbursement or the Cancer Drugs Fund. Only applying the cost of chemotherapy may introduce bias if more efficacious treatment than chemotherapy

was administered to patients at subsequent lines of treatment which was captured within OS in the model, but a smaller cost associated with treatment is applied.

Table 14 and Table 15 show the results when chemotherapy cost is applied to the entire proportion of patients receiving inotuzumab or blinatumomab as subsequent treatment at 1.5% and 3.5% discount results respectively. As shown when applying the 1.5% discount rate, inotuzumab is still a cost-effective option in comparison to standard of care (SoC) at a £50,000 willingness to pay threshold.

Table 264: Scenario analysis assuming costs applied to patients receiving blinatumomab and inotuzumab are replaced with costs of chemotherapy (1.5% discount)

Input	Base case	Scenario	ICER
Subsequent treatment	No scenario analysis	Chemotherapy costs applied to patients receiving blinatumomab and inotuzumab	£44,082
Key: ICER, incremental cost-effectiveness ratio			

Table 275: Scenario analysis assuming costs applied to patients receiving blinatumomab and inotuzumab are replaced with costs of chemotherapy (3.5% discount)

Input	Base case	Scenario	ICER
Subsequent treatment	No scenario analysis	Chemotherapy costs applied to patients receiving blinatumomab and inotuzumab	£61,594
Key: ICER, incremental cost-effectiveness ratio			

B10. The “end of life” costs applied in the model appear specific to cancer patients over their last 12 months of life. Please provide further justification for the appropriateness of this estimate applied in the pre and post-cure periods (i.e. whether it is reasonable to apply costs derived over a 12 month period given the short life expectancy of many patients and whether it is appropriate to assign cancer costs to mortality events in the post-cure period).

Pfizer response:

The “end of life” costs applied for patients who die beyond the 3-year cure point were assumed to incur the same cost as patients who died before the cure point due to

uncertainty of causes of death beyond the cure point. This was seen as a simplifying assumption.

Based on 2011 data, 29% of all deaths within the UK are a result of cancer [1], and therefore even if patients are cured of R/R B-cell ALL following HSCT, there is still a large probability that a patients' death in the cured health state will still be a result of cancer whereby the cost assigned would be appropriate.

Further to this, the PSSRU[2] reports an end of life cost relevant for patients that had no diagnoses and any diagnoses in the final year of life. These were £8,038 and £12,015 respectively. The end of life cost specific to cancer (£11,616) patients lays between the two values and therefore again seemed an appropriate value to apply to represent the general population where some causes of death would be known while others not.

Three additional scenarios are supplied below which:

1. Apply a zero-cost associated with the end of life for post-HSCT patients after the 3-year cure point

2. Apply a 'no-diagnoses' end of life cost for patients for post-HSCT after the 3-year cure point (£8,038)

3. Apply an 'any diagnoses' end of life cost for patients post-HSCT after the 3-year cure point (£12,015).

The results of these scenarios when applying a 1.5% discount rate for costs and QALYs are shown in Table 16 and results using a discount rate of 3.5% for costs and QALYs are shown in Table 17. Overall the model is relatively insensitive to these changes with lower corresponding ICERs when no cost, or the cost associated with no diagnoses are considered. When applying the cost of any diagnoses as the end of life cost (£12,015), the difference in the ICER from the base case was minimal, with only a £10 difference in the results where 1.5% discount rates are incorporated and £4 when the 3.5% discount rates are applied.

Table 286: Scenario analysis changing the end of life cost post cure point for patients post-HSCT (1.5% discount)

Input	Scenario	ICER
End of life costs	Base case	£40,013
	Apply no EOL cost post cure point	£39,710
	Apply non-diagnoses EOL cost post cure point	£39,920
	Apply an any-diagnoses EOL cost post cure point	£40,023
Key: EOL, End of Life. ICER, Incremental cost-effectiveness ratio		

Table 17: Scenario analysis changing the end of life cost post cure point for patients post-HSCT (3.5% discount)

Input	Scenario	ICER
End of life costs	Base case	£55,869
	Apply no EOL cost post cure point	£55,733
	Apply non-cancer specific EOL cost post cure point	£55,827
	Apply an any-diagnoses EOL cost post cure point	£55,873
Key: EOL, End of Life. ICER, Incremental cost-effectiveness ratio		

References

1. Cancer Research UK. Cancer mortality statistics. 2011. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality Accessed: 10 March 2017.
2. Curtis LB, A. . Unit Costs of Health and Social Care 2016. 2016. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php.

B11. Please provide further clarification regarding how the post-HSCT utility values were derived from the reference provided (Kurosawa, 2015).

Pfizer response:

Please note that the reference Kurosawa et al, 2015 [1] was not used to derive utility values within the economic model. This was an error in referencing. Instead the correct reference for utilities for the post HSCT health state is Kurosawa et al, 2016 [2].
Kurosawa et al, 2016 performed a decision analysis comparing allogenic HCT versus chemotherapy for patients with acute myeloid leukaemia (AML) [2]. Adjusted means of the EQ-5D scores were used as quality of life estimates adopted from their previous cross sectional study of AML survivors, Kurosawa 2015 [1]. The utilities derived in Kurosawa 2016 and applied within the model as the utility values associated with post-HSCT are shown in Table 1 of the reference (provided alongside this response). The study reported utility values for patients live hematopoietic cell transplantation (HCT) for time periods less than one year, between one to two years, between three to five year and greater than five years.[2]
Reference

[1] Kurosawa S, Yamaguchi T, Mori T, et al. Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. *Bone Marrow Transplantation*. 2015; 50(9):1241-9.

[2] Kurosawa S, Yamaguchi H, Yamaguchi T, et al. Decision Analysis of Postremission Therapy in Cytogenetically Intermediate-Risk Acute Myeloid Leukemia: The Impact of FLT3 Internal Tandem Duplication, Nucleophosmin, and

CCAAT/Enhancer Binding Protein Alpha. *Biology of Blood and Marrow Transplantation*. 2016; 22(6):1125-32.

B12. The costs sheet in cell E101 ("Outpatient: Deliver Complex Chemotherapy") references SB13Z NHS Reference Costs 15/16. Please confirm whether this is the correct reference or whether this should refer to SB14Z? The ERG have not been able to validate this unit cost estimate based on checks of the Reference Costs. Please confirm that the correct unit cost has been applied.

Pfizer response:

The correct reference for the outpatient cost is Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, SB14Z – Outpatient from NHS reference costs 2015-2016. Therefore, the cost applied within the model was correct but the code was mislabelled.

An alternative scenario is presented below which shows the effect on the ICER if the SB13Z, Deliver more Complex Parenteral Chemotherapy at First Attendance – Outpatient was used for the cost of administration. Table 18 shows the results when a 1.5% discount rate is applied to costs and QALYs, while Table 19 shows the results when a 3.5% discount rate is applied. In both scenarios, the ICER is reduced from the base case by £144 and £203 respectively.

Table 18: Scenario analysis using alternative outpatient reference cost (1.5% discount)

Input	Scenario	ICER
Outpatient cost	SB14Z	£40,013
	SB13Z	£39,869

Table 19: Scenario analysis using alternative outpatient reference cost (3.5% discount)

Input	Scenario	ICER
Outpatient cost	SB14Z	£55,869
	SB13Z	£55,666

B13. **Priority question**: Please confirm whether the acquisition cost for inotuzumab stated in the company submission is the final list price.

Pfizer response:

The list price stated in the submission [redacted] is the anticipated list price. However, the list price is not final until it is approved by the Department of Health, which is expected to happen nearer to the time of marketing authorisation. The anticipated European marketing authorisation date is July 2017.

Section C: Textual clarifications and additional points

C1. **Priority question:** On page 116 of the company submission it states that the only groups which did not display significant rate differences were for patients with Philadelphia chromosome positive (Ph+) disease and patients with chromosome translocation (4:11) positive disease. Please clarify whether this statement is referring to Figure 15 on page 116 or Figure 16 on page 118. In addition, please present a commentary and p-values for Figure 16.

Pfizer response:

The text in question on page 116 was incorrectly included under the heading "Pre-specified OS – subgroup analysis" and should have remained as part of the previous section, which is under the heading "CR/CRi – subgroup analysis".

This text (copied below for ease of reference) confirms the results shown in Figure 15 of the submission; the CR/CRi rate differences in the Ph+ and t(4;11) subgroups are shown to be non-significant.

The rate differences and patient numbers included in the text below come from Table 14.2.1.4 in the sCSR (CR/CRi analysis in Ph+ and t(4;11) patient subgroups in the ITT population per Investigator assessment), which now accompanies this response.

> "In terms of baseline cytogenetic characteristics, the only groups which did not display significant rate differences were for Ph+ patients (rate difference: [redacted]) and t(4:11) patients (rate difference: [redacted]). However, both of these subgroups contained extremely small numbers of patients (6 vs 7 for inotuzumab vs control patients and 22 vs 28 for inotuzumab vs control patients, in the t(4:11) and Ph+ subgroups, respectively) and therefore interpretation of the data is limited".

In Figure 15 of the company submission dossier, the data are based on CR/CRi per Endpoint Adjudication Committee (EAC) (primary endpoint) in the intent to treat population in the initial 218 patients randomized (ITT218 population). CR/CRi per EAC were only assessed and analysed in the ITT218 population (per protocol). In Study B1931022 sCSR Table 14.2.1.4, the data are based on CR/CRi per Investigator in the intent to treat population in all 326 patients randomized (ITT population).

Figure 1 of this response shows the Forest Plot of overall survival for all patients and key subgroups in the ITT population (Figure 16 of the submission), now with both 1-sided and 2-sided p-values. As stated in the submission, a comparison of the medians is not reflective of the whole survival distribution, due to the separation in the tails of the curves; these results should be interpreted with caution.

[redacted]

Figure 1: [redacted]

Source: Study B1931022 Figure 544.C1

Figure 1 (continued): [redacted]

Figure 1 (continued): [redacted]

Source: Study B1931022 Figure 544.C1

SUPPORTING DOCUMENTATION

Study B1931022 Figure 544.C1

Study B1931022 sCSR Table 14.2.1.4

C2. **Priority question:** On page 109 it states that baseline pain scores favoured inotuzumab, but in Table 28 (page 110) pain scores are identical in the inotuzumab and SOC group. Please clarify whether the figures in Table 28 are correct.

Pfizer response:

The correct results for the EORTC QLQ-C30 domains of nausea and vomiting and pain are presented in Table 20.

Table 290: PRO at baseline in INO-VATE 1022 (ITT population)

Characteristics	Inotuzumab (N = 164)	SoC (N = 162)
	Mean (SE)	Mean (SE)
EORTC QLQ-C30		
Nausea and vomiting	[redacted]	[redacted]
Pain	[redacted]	[redacted]

C3. Page 80 describes the competing risk analysis. Please confirm whether the category 'death due to other causes' (excluding relapsed or refractory [R/R] B-cell ALL) also excluded death due to VOD and other adverse events of treatment for R/R B-cell ALL.

Pfizer response:

'Death due to other causes' means death due to causes other than relapse. Therefore this does include death due to VOD and other adverse events as these are not relapse.

C4. The Advisory Board in the R/R B-Cell ALL report is referenced throughout the company submission. The names, roles and expertise of experts at the advisory board meeting have been removed. Please provide details of the expertise of the advisors, so that the ERG can assess the reliability/applicability of this report.

Pfizer response:

The list of advisory board attendees, their role and expertise is included in Table 21 below.

Table 21: List of attendees present at the advisory board meeting

Name of attendee	Role and expertise
Experts	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

C5. Please explain why adverse event results for stomatitis and dyspepsia are reported as ‘not applicable’ for ‘all cycles’ in Table 33 on page 132.

Pfizer response:

The adverse event results for stomatitis and dyspepsia are only presented in the CSR for cycle one and not for all cycles. These should be presented as “not reported” (NR) within Table 33.

C6. Please explain apparent inconsistencies in patient numbers between Tables 22 and 23 (pages 100 and 101) (e.g. 22 minimal residual disease [MRD]+ vs 41 MRD+, 92 MRD- vs 97 MRD- for inotuzumab group, and similar inconsistencies in the SoC group).

Pfizer response:

In Table 22, MRD-positive is for patients who achieved CR/CRi. In Figure 4 MRD-positive is for all patients regardless of whether they achieved CR/CRi.

C7. Please clarify whether there is a typographical error in Table 13. The total number of treated patients in the SoC group = 1 + 128 + 15 = 144, however the total SoC population = 143.

Pfizer response:

In Table 13, the groups under the 'treated' category are not mutually exclusive, i.e., the 1 patient designated as 'completed treatment' was part of the subgroup for 'discontinued from study'.

C8. Please clarify whether there are any inconsistencies between Figures 14 and 15 on page 116 and Table 14 on page 88.

Pfizer response:

The data for age, salvage status and duration of first remission in Figures 14 is based on data using the interactive voice recognition system (IVRS) whereas the data in Table 14 is based on data using the case report form (CRF).

In Figure 15, the data is based on a cutoff of 02 October 2014 whereas the data cutoff for data in Table 14 is based on a cutoff of 08 March 2016.

Searching

C9. Please clarify whether any trial registers were searched for ongoing or recently completed trials of inotuzumab ozogamicin or the other drugs used to treat ALL listed in table 8, on page 65. If so, please provide details of which trial registers were searched, the date of the search and the search strategy used.

Pfizer response:

Trial registry searches were not performed as part of the submission.

C10. It is stated that an English language limit has been applied to the searches of MEDLINE and Embase in Appendix 2, Table 1, page 8 at line 43, giving 7856 results. However section 4.1.1., page 63 of the company submission states that studies published in non-English languages were included in the systematic literature review and flagged. Please clarify which statement is correct and also whether studies published in non-English languages where included in the cost-effectiveness searches, reported in Appendix 3.

Pfizer response:

The objective of the SLR was to include studies published in English language only. Therefore a filter for English language studies was applied at the database searching stage. This functionally was available in the Embase database only. However, this still led to the retrieval of a small number of non-English articles in the SLR searches, despite this restriction. As there was no intent to extract any data from non-English studies, they were excluded at the full text screening stage.

C11. In the PRISMA flow diagram on page 68, 8554 records are reported as identified through the database searching. The 8554 results reported suggests that the search results from MEDLINE and Embase had an English language limit applied. Please

clarify that 8554 the correct figure for the results identified through database searching. Should it be higher than this if any non-English language results were identified and were then screened for possible inclusion in the review? Please also clarify whether studies published in non-English languages where include for the cost-effectiveness searches, reported on page 154

Pfizer response:

The PRISMA flow diagram is accurate.

The objective of the SLR was to include studies published in English language only. Therefore a filter for English language studies was applied at the database searching stage. This functionally was available in the Embase database only. However, this still led to the retrieval of a small number of non-English articles in the SLR searches, despite this restriction. As there was no intent to extract any data from non-English studies, they were excluded at the full text screening stage.

C12. Please provide details of the source for the study design search filters used in Table 1, pages 7-8, (search lines 34 and 35) in Appendix 2?

Pfizer response:

The filters (RCTs as well as nRCTs) have been developed based on the terms mentioned in the SIGN (Scottish Intercollegiate Guidelines Network) filter.

Link to Sign filter: http://www.sign.ac.uk/methodology/filters.html#random

C13. The title of Appendix 2 refers to identifying safety and health-related quality of life data as well as clinical effectiveness data. Please clarify whether this is correct?

Pfizer response:

Appendix 2 provides the search strategies for clinical SLR. The objective of clinical SLR was to evaluate effectiveness, safety and health-related quality among the patients receiving intervention of interest thereby this title is correct.

Additional note from Pfizer:

Please note that a minor correction is required to the model. This is in relation to the administration costs associated with the standard of care. The correction is within the proportion of patients receiving cycle 2 of treatment for CM and HIDAC, where the proportion receiving treatment was linked to FLAG as opposed to CM/HIDAC. The correction is specified below:

- Sheet “Resource use” Cell E41 should read “='Resource use'!D41/'Resource use'!D40”

- Sheet “Resource use” Cell E49 should read “='Resource use'!D49/'Resource use'!D48”

The results of this correction are negligible, as it lowers the initial base case by £64. Given the small difference from the base case, Pfizer have kept results presented within this clarification response in line with the original model submitted to NICE.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over eight key areas:

- 24-hour CARE Line
- Nurse Advisor Service
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes emotional effects of a blood cancer and help for those caring for a patient. Our focus is providing

information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc.

Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/resources/code-of-practice

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. In 2014, there were 758 new cases of acute lymphoblastic leukaemia in the UK. Approximately 60% of these cases were diagnosed in children and teenagers. Most of the remaining 300 cases were diagnosed in adults over the age of 50.

This submission is informed by a patient experience survey of 151 adults diagnosed with ALL, carried out by Leukaemia CARE.

Symptoms experienced prior to diagnosis include fatigue (69%); feeling weak or breathless (61%), fever or night sweats (36%), bruising or bleeding (31%), pain in bones or joints (28%), unexplained weight loss (26%), sleeping problems (26%) and swollen lymph nodes (22%). Due to the rapidly progressing nature of the condition, 63% of patients had experienced symptoms for less than a month before visiting their GP.

The NCIN/NCRAS routes to diagnosis report shows that 64% of ALL patients are diagnosed via emergency presentation (of which 42% were A&E, 27% emergency GP referral, 5% inpatient emergency and 26% outpatient emergency). This compares to a cancer average of 22% and is the highest of any cancer type in the report. The rapidly progressing nature of the condition means that 86% of ALL patients start treatment within a week of diagnosis.

Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. In our survey, 60% of ALL patients reported that they have felt depressed or anxious more often since their diagnosis.

The emotional impact does not affect the patient in isolation and is often also felt by carers and family members. This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis. As

such, improvements in a patients' treatment and quality of life will also have a wider impact on the lives of their family and friends.

The most common symptoms encountered by patients since their diagnosis are fatigue (76%), feeling weak or breathless (54%), sleeping problems (53%), nausea or vomiting (45%), memory loss or loss of concentration (44%), tingling or numbness in extremities (44%), bone or joint pain (38%), bleeding or bruising (38%) and infections (36%).

ALL also has a much wider practical impact, with 64% of ALL patients experiencing pain as a direct result of their condition (30% occasionally, 24% regularly and 9% constantly). Additionally, 62% of ALL patients have difficulty moving around (sometimes 32%, often 18% and always 11%) and 65% of ALL patients have difficulty performing some of their daily routines, such as cooking or cleaning. Another 48% reported that they have problems taking care of themselves (sometimes 31%, often 11% or unable to self-care at all 6%). Of those in work or education before their diagnosis, 70% have been impacted (31% reduced hours, 39% no longer able to work or continue education). Consequently, 60% of ALL patients reported a negative financial impact as a result of having cancer (increased costs or reduced income).

Five-year survival outcomes vary greatly by age, from over 90% in the under 14s, almost 70% in those aged 15-24, less than 40% in those aged 25-64 and less than 15% in those aged 64 or older. As such, the prognosis for adult patients with ALL is extremely poor.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

When asked what they considered to be important features of a new treatment, ALL patients listed: improved or longer survival (84%), improved quality of life (77%), tolerable side effects (64%), a remission or response (62%), a reduced impact on carers or family members (48%) and improved blood counts or test results (47%).

When asked if they would consider it positive for a treatment to subsequently enable them to have a stem cell transplant, 91% said yes.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Whilst highly toxic chemotherapies have high response rates (80-90%), nearly half of patients will eventually relapse. In the relapsed or refractory setting, survival outcomes are poor, with a five-year survival rate for relapsed patients of less than 10%. This demonstrates the urgent need for effective salvage treatment options.

There is currently no standard of care in this setting, with treatment options including salvage chemotherapy (FLAG and G-CSF; Hyper CVAD, HIDAC or cytarabine and mitoxantrone) or potentially blinatumomab. There is also a small minority eligible for stem cell transplantation or clinical trials. However, allo-SCT is the most effective and therapeutic option relapsed and refractory ALL patients.

For patients treated with chemotherapy at first relapse the median overall survival is around 5-9 months, for those who have failed multiple lines of therapy overall survival decreases to around 3-6 months.

The most common side effects reported by ALL patients were fatigue (74%), neutropenia (44%), nausea or vomiting (44%), hair loss (42%), muscle or joint pain (41%), sore mouth (40%), sleeping problems (38%), loss of concentration or memory (37%), diarrhoea (32%), bone and joint pain (32%). The combined impact of these side effects was rated by 52% as having had a large impact, with 51% of patients hospitalised as a result of side effects.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain

- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Inotuzumab appears to offer the following benefits:

- improved survival – median progression-free survival (PFS) was improved as was mean overall survival (OS)
- a remission or response – significantly more patients attain complete remission with inotuzumab, with more durable remissions
- improved blood counts or test results – significantly more patients achieved minimal residual disease
- bridge to transplant – significantly more patients were able to proceed to transplant following treatment with inotuzumab – a significant benefit

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See above

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

- Side effects - The most common side effects reported by ALL patients were fatigue (74%), neutropenia (44%), nausea or vomiting (44%), hair loss (42%), muscle or joint pain (41%), sore mouth (40%), sleeping problems (38%), loss of concentration or memory (37%), diarrhoea (32%), bone and joint pain (32%). The combined impact of these side effects was rated by 52% as having had a large impact, with 51% of patients hospitalised as a result of side effects.

- As already indicated, there are currently very limited treatment options available for relapsed or refractory ALL patients, with most patients unable to have an allogenic stem cell transplant.

Please list any concerns patients or carers have about the treatment being appraised.

- Potential side effects – such as veno-occlusive liver diease

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

Leukaemia CARE patient experience survey of 151 acute lymphoblastic leukaemia patients, unpublished. This was part of a wider survey of over 2,500 blood cancer patients undertaken between September and December 2016.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. ALL is often diagnosed as an emergency (64%), with 86% of patients starting treatment within a week of diagnosis.
- It also has a significant symptom burden (fatigue, breathlessness, sleeping problems, nausea, vomiting, memory loss, pain), as well as a financial and emotional impact.
- Treatment options are limited, most likely to salvage chemotherapy. Only a small proportion of patients would currently be eligible for allo-SCT, the only curative option, offering the most effective and durable disease control. Overall survival in this setting is limited, usually a matter of months. Five-year survival rates are less than 10%.
- Inotuzumab ozogamicin offers a number of potential benefits, including improved response rates and longer survival (PFS and mean OS).
- Another key benefit of inotuzumab ozogamicin is its potential as a bridge to transplant, the only curative option for these patients. This was welcomed by 91% of ALL patients in our recent survey.

Submission by NHS England re the NICE appraisal of inotuzumab ozogamicin in the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL)

1. The aim of salvage treatment for relapsed/refractory ALL is to either induce a durable complete remission or to maximise the rate of subsequent high-dose chemotherapy and stem cell transplantation (SCT) [and in this case an allogeneic SCT].

2. There are two new monoclonal antibodies that have recent phase 3 evidence as to their benefit in relapsed/refractory ALL: blinatumomab which has recently been recommended by NICE and inotuzumab ozogamicin in this appraisal. The case mix of the patients entering the 2 trials is not the same as the patients in the blinatumomab trial were more heavily pre-treated. The 2 drugs have different modes of action. They have different schedules of administration (inotuzumab is much easier to deliver as it is a 1 hour weekly infusion given in 3 week cycles and blinatumomab requires a continuous intravenous infusion for 4 weeks per 6 week cycle of therapy and also requires an initial inpatient stay). These 2 drugs have different major toxicities (cytokine release syndrome, tumour lysis syndrome and neurotoxicity with blinatumomab and veno-occlusive disease with inotuzumab). Blinatumomab is currently licensed only in Philadelphia chromosome negative ALL whereas inotuzumab is expected to be licensed in both Philadelphia chromosome +ve and –ve ALL.

3. The inotuzumab INOVATE trial was in adults and used a comparator which was a choice of 3 main chemotherapy regimens, this partially reflecting the different treatments which patients had previously received and the fact that no one salvage treatment has been shown to be superior to another. 65% of patients were at 1st relapse and 18% of patients had previously undergone an allogeneic SCT.

4. The overall survival data for the INOVATE trial is immature as there are few patients at risk beyond 15-20 months after randomisation. The key issues are at which survival levels the overall survival curves truly plateau at and what the difference is between inotuzumab and standard chemotherapy.

5. The level of cross over from the chemotherapy arm to subsequent inotuzumab was low at 4% and blinatumomab usage in the chemotherapy arm was modest at 11% ie cross over and blinatumomab use are unlikely to have had a major confounding effect on the survival results.

6. There is no doubt that inotuzumab significantly increased the rate of complete remission with or without full blood count recovery (73% vs 31% on ITT analysis). Of note also is that the rate of subsequent allogeneic SCT was 43% vs 11%.

7. NHS England notes the differing toxicity of inotuzumab vs that of chemotherapy and the known risk of veno-occlusive disease. It is confident that continued experience with the use of inotuzumab would minimise the risk of subsequent veno-occlusive disease.

8. NHS England notes that the economic model assumes that patients alive at 3 years then revert back to population norm figures for life expectancy. This is incorrect as ALL survivors continue to be at increased risk of long term mortality.

9. NHS England notes that imatinib is used in the economic model as part of treatment for patients with relapsed/refractory Philadelphia +ve ALL. This is despite the INOVATE trial requiring Philadelphia +ve patients to have previously been treated with at least one second generation tyrosine kinase inhibitor. NHS England notes that the cost of imatinib used in the economic model is the list price for the branded drug: this price no longer applies as the drug now has several generic versions.

10. NHS England notes that the probabilistic ICERs for inotuzumab are significantly higher than the deterministic ones.

11. The management of patients with relapsed/refractory ALL is a specialist practice, the numbers of patients are small and the administration of inotuzumab is mainly aimed at quickly moving to stem cell transplantation if possible. NHS England would therefore wish inotuzomab to be used only in large centres which regularly assess and treat such relapsed ALL patients.

12. NHS England notes that the license for inotuzumab is likely to restrict use to patients aged 18 and over. There is no biologically plausible reason as to why inotuzumab would not have similar activity in children as seen in adults. If NICE recommends the use of inotuzumab within its expected marketing authorisation, NHS England would potentially wish to commission its use in patients of less than 18 years in age, subject to NHS England ascertaining the impact of such a decision on currently running clinical trials.

[redacted]

[redacted]

5 May 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Prof Adele K. Fielding

Name of your organisation

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no national guidelines for the therapy of relapsed ALL. This is, at least in part because we have hitherto have had to rely (in *BCR-ABL1*/Philadelphia chromosome negative ALL) upon relatively ineffective and highly toxic regimens of combination chemotherapy composed largely of agents used during the initial therapy of ALL. For patients with *BCR-ABL1*/Philadelphia chromosome positive ALL, targeted oral agents - tyrosine kinase inhibitors - can be successfully employed to obtain remissions at relapse; however agents such as dasatinib are not reimbursed in the NHS and ponatinib is only reimbursed in very specific and relatively rare circumstances.

The overall goal of treatment of relapsed ALL in adults is long term disease-free survival equating to 'cure'. This is not common, but remains formally possible.
The steps to this taken by most centres, based on the published literature, as opposed to specific guidance, are

1. To achieve complete remission (CR). It is worth noting that the definition of CR is strict – fewer than 5% leukaemic blasts in the bone marrow accompanied by adequate peripheral blood counts with neutrophils and

platelets being the critical cells. There are other definitions of response such as CRi (CR with incomplete haematopoetic recovery) the predictive meaning of which is not clear; they may relate simply to the protocol-related timing of the assesement or they may relate to toxicity of the agent on the bone marrow, or impending relapse. Increasingly, publications in relapsed ALL refer to the quantification of minimal residual disease which is a measure of 'deep' response and is a predictive biomarker for outcome in de novo ALL. It should be noted that the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED.

2. **To achieve an allogeneic bone marrow transplant wherever possible.** It is a pre-requisite in most countries for CR to be obtained prior to allograft. Many countries do allow/fund second allograft, but this is rare in the UK. Allograft is currently thought to be the only curative option.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Inotuzumab ozogamicin (IO) is a new agent in the therapy of ALL. To understand the potential value of a novel agent such as inotuzumab, it is necessary to look at the known prognostic subgroups of patients who can benefit as well as the benefit to the group as a whole.

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There are numerous papers which clearly summarise the poor outcome of ALL after relapse and detail the major prognostic factors for survival in this situation. Listed below are the main prognostic factors for outcome after relapse.

- Early relapse (within 1 -2 years of diagnosis)
- Relapse after allograft
- Older patients in relapse
- Second or subsequent relapse

The drug IO seems to show **benefit in remission rate and in survival; importantly, the benefit applies even in some of the worst prognostic groups**.

Ease of delivery – the drug IO is easily delivered, by weekly injection, including the possibility to treat on an out-patient basis, whereas the combination chemotherapy drugs used often necessitate inpatient stays lasting several weeks

Relative lack of side effects compared to combination chemotherapy – the agent is well tolerated. The SAE and AE profile as reported in formal trials can be hard to interpret as patients often already have deranged bone marrow function due to the underlying disease; infections and so on are common place.

A **particular adverse effect of potential concern is veno-occlusive disease of the liver** (VOD). VOD is a rare event seen almost exclusively after bone marrow allograft. There was a higher than expected rate of this rare event in some patients who subsequently received allograft. These patients had been pre-treated (conditioned) with a combination of alkylating agents “dual alkylator conditioning” not typically used in the UK. Outside of these circumstances – which can be readily avoided – VOD does not seem to be much of an issue.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

None known

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Single Technology Appraisal (STA)

None known

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The agent is easy to administer requiring less time and skill to prescribe, administer and monitor than complex standard of care regimens
Patients can receive the agent as out patients if they have no other reason for inpatient hospitalisation

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Single Technology Appraisal (STA)

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Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

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Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor David Marks

Name of your organisation [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?YES. NCRI ALL GROUP
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The proposed use of Inotuzumab is in relapsed or refractory acute lymphoblastic leukaemia. This is most commonly treated with FLAG or FLAG Ida but sometimes with other regimens involving high-dose Ara-C or Clofarabine. There is some slight variation in current practice but the most common regimens are FLAG based. The current salvage chemotherapy has a low chance of success and is extremely toxic almost always causing bacterial and sometimes fungal infections. Outcomes vary depending usually on when a patient relapses. If they relapse during chemotherapy for ALL the chance of getting them back into remission is lower and the chance of curing them very low. If they have relapsed having stopped therapy the chance of curing them is higher. Patients with adverse cytogenetics do worse. The setting for Inotuzumab would be at major haemato/oncology units that look after acute lymphoblastic leukaemia. The drug would be given by consultants who specialise in acute leukaemia care and they would need the input of the whole leukaemia team including clinical nurse specialists. Inotuzumab is not available outside of clinical trials or on compassionate use. There are no relevant clinical guidelines for relapsed ALL and no standard of care.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The main advantage of Inotuzumab is that it achieves a much higher remission rate in relapsed ALL. In the Inovate study the standard complete remission rate of 30% was increased to about 80% and this was highly statistically significant. There is also improvement in survival using restricted means survival time analysis. This improved RMST from 9.9 months to 13.9 months and this was highly significant. The other advantage of Inotuzumab is that it can be given in an outpatient setting and most patients do not require hospital admission. There is some infusional toxicity. It needs to be probably given to patients with CD 22 positive ALL but that is more than 90-95% of cases. The Inovate study published in the new England Journal is not entirely applicable to a UK setting.

The major side effect of Inotuzumab is an increased chance of veno-occlusive disease. This was 11% in the Inotuzumab arm and 1% in the standard of care arm. After transplant the incidence of veno-occlusive disease was 21% and there were some cases of fatal veno-occlusive disease. Patients who have prior liver function test abnormalities are less suitable for receiving Inotuzumab therapy. The therapy may also be more toxic when given after an allograft, especially if there is hepatic dysfunction. Within the trial some of the patients who got veno-occlusive disease had 2nd transplants. As NICE may be aware 2nd transplant is not possible within the United Kingdom because it is not commissioned.

Equality and Diversity

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- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NO ISSUES

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Other outcomes

Progression free survival was increased from 1.8-5 months and that was highly significant. The Improvement in overall survival using conventional methods was only one month but it was entirely reasonable to use restricted mean survival time as an estimate of the benefit of the drug. There appears to be a plateau after about 18 months and this is the experience in 2nd remission transplant that if you survive the first 18 months your likely to be cured. It currently looks that about one quarter of patients are candidates to be cured. The only other thing that is worth mentioning in the trial is that there was a lower incidence of episodes of febrile neutropaenia which is consistent with the finding that this drug can be given as an outpatient. We need more experience of the hepatotoxicity of Inotuzumab outside clinical trials but Pfizer will have some data from the compassionate use of the drug which has been a very successful programme. In my Centre we have given the drug to seven adult patients and there has been no significant hepatotoxicity.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group's Report
Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

Authors
Ros Wade, Research Fellow, CRD
Edward Cox, NIHR Research Methods Fellow, CHE
Mathilde Peron, Research Fellow, CHE
Kristina Charlotte Dietz, NIHR Research Training Fellow, CRD
Melissa Harden, Information Specialist, CRD
Alison Eastwood, Professor of Research, CRD
Stephen Palmer, Professor of Health Economics, CHE
Susan Griffin, Senior Research Fellow, CHE

Correspondence to Ros Wade, Research Fellow, CRD, University of York, York YO10 5DD

Date completed 12/04/2017

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Declared competing interests of the authors
None.

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We would like to thank Dr Nick Morley, Consultant Haematologist at the Royal Hallamshire Hospital in Sheffield for clinical advice throughout the project. In addition, Mark Simmonds, Centre for Reviews and Dissemination, for statistical advice.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Ros Wade wrote the clinical effectiveness sections of the report, with assistance from Kristina Dietz. Edward Cox wrote the cost effectiveness section of the report and conducted the economic analyses, with assistance from Mathilde Peron. Melissa Harden wrote the sections on the search strategies. Alison Eastwood commented on drafts of the report and took overall responsibility for the clinical effectiveness sections of the report. Stephen Palmer provided advice and commented on drafts of the report. Susan Griffin wrote the additional cost effectiveness analyses and commented on drafts of the report and took overall responsibility for the cost effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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List of abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
BSC	Best supportive care
CDF	Cancer Drugs Fund
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CM	Cytarabine plus mitoxantrone
CR	Complete response
CRi	Complete response with incomplete count recovery
CS	Company's submission
CSR	Clinical study report
DoR	Duration of remission
EAC	Endpoint Adjudication Committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQol 5-dimension questionnaire
EQ-VAS	EuroQol visual analogue scale
ERG	Evidence Review Group
FLAG	Fludarabine, cytarabine and granulocyte-colony stimulating factor
FLAG-IDA	FLAG plus idarubicin
GvHD	Graft versus host disease
HIDAC	High dose cytarabine
HR	Hazard ratio
HRQoL	Health related quality of life
HSCT	Haematopoietic stem cell transplant
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IDA	Idarubicin
ITT	Intention-to-treat

IVRS	Interactive Voice Response System
KM	Kaplan-Meier
MDACC	MD Anderson Cancer Center
MRD	Minimal residual disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office for National Statistics
OS	Overall survival
PFS	Progression-free survival
PH	Proportional hazards
Ph+/-	Philadelphia chromosome positive/negative
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RMST	Restricted mean survival time
R/R	Relapsed or refractory
SAE	Severe adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
SPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TTO	Time trade off
VOD	Veno-occlusive liver disease

1 Summary

1.1 Critique of the decision problem in the company's submission

The population in the company submission (CS) matched that specified in the NICE scope: adults with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL). However, the CS stated that "inotuzumab is suitable as a bridge to potentially curative therapy (usually haematopoietic stem cell transplant (HSCT)), patients who are unfit for intensive therapy, such as chemotherapy-based treatments, will also be unfit for transplantation. Therefore, inotuzumab would also be unsuitable for these patients". Consequently, only a subset of adults with R/R B-cell ALL would be suitable for inotuzumab in clinical practice; those who are fit for intensive therapy, such as chemotherapy-based treatments and transplantation. The anticipated licenced population, defined in the draft Summary of Product Characteristics, is the broader population of "[redacted]".

The clinical effectiveness evidence presented is primarily from the INO-VATE 1022 trial, in which the population comprised only the subset of patients who were suitable for intensive therapy: "relapsed or refractory CD22-positive ALL due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option"; therefore patients who would be treated with palliative intent were not eligible for the trial, nor were patients who were due to receive salvage therapies beyond Salvage 2.

The intervention in the CS matched that specified in the NICE scope. However, some of the comparators listed in the NICE scope (clofarabine-based combination chemotherapy for Philadelphia chromosome (Ph) negative patients and tyrosine kinase inhibitors (TKIs) alone or in combination with clofarabine-based chemotherapy for Ph positive patients) were not included in the submission; these treatments are used in UK clinical practice so should have been included as comparators in the CS. The NICE scope also included a "best supportive care (including palliative care)" comparator, for people who are unable to tolerate chemotherapy. However, as stated previously, patients who are unfit for intensive therapy were not included in the submission or the INO-VATE 1022 trial. Two of the comparators used in the INO-VATE 1022 trial were chemotherapy regimens that are not used in current NHS practice and were not listed in the NICE scope (cytarabine plus mitoxantrone (CM) and high dose cytarabine (HIDAC)), although the majority of patients in the standard of care (SoC) arm of the trial received fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based chemotherapy, which is used in NHS practice.

The outcomes listed in the NICE scope were reported in the CS, with the addition of two further outcomes: minimal residual disease (MRD) negativity and rate of potentially curative therapy, such as HSCT. Both of the additional outcomes appear to be appropriate, they are surrogate outcomes associated with improved patient survival after potentially curative therapy. However, the clinical expert statement submitted by Professor Adele Fielding emphasised that "the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED", therefore, the results relating to MRD negativity should be interpreted with caution, particularly for patients receiving second salvage treatment, for whom MRD negativity has not been shown to be associated with better survival outcomes.[1]

1.2 Summary of clinical effectiveness evidence submitted by the company

The company described a systematic review of comparative studies of specified interventions used in the treatment of R/R B-cell ALL.

The evidence presented in the CS was primarily based on one reasonably good quality RCT; the INO-VATE 1022 trial, which compared inotuzumab to SoC, which was the investigator's choice of FLAG, CM or HIDAC. The trial demonstrated that inotuzumab confers significant benefits in terms of achieving a complete response or complete response with incomplete count recovery (CR/CRi), meeting the primary objective of the trial. A total of [redacted] inotuzumab patients achieved CR/CRi compared with [redacted] SoC patients; of which a significantly greater proportion in the inotuzumab arm also achieved MRD negativity compared with the SoC arm. For patients who achieved CR/CRi, the median duration of remission (DoR) was [redacted] months (95% CI: [redacted]) in the inotuzumab group and [redacted] months (95% CI: [redacted]) in the SoC group. The median time from randomisation to achieving CR/CRi was [redacted] months (range [redacted] months) in the inotuzumab group and [redacted] months (range [redacted] months) in the SoC group.

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; [redacted] The total number of patients that had an HSCT, regardless of their remission status, time of transplant and whether it was received prior to any post-induction therapy was [redacted] in the inotuzumab group and [redacted] in the SoC group.

The median overall survival (OS) was 7.7 months (95% 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 boundary of P=0.0208. However, the CS stated that the OS data appeared to deviate

from the proportional hazards assumption at around 15 months with the separation of curves in the Kaplan-Meier plots appearing after the median had been reached. Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. The difference in OS between treatment groups [redacted]. The RMST analysis results presented in the CS were those for the truncation time of 37.7 months; median OS in the inotuzumab group was 13.9 months (standard error (SE): 1.1) and for SoC 9.9 months (SE: 0.9), with a difference of 3.9 months between groups (95% CI: 1.2 to 6.7).

The data presented indicated a greater 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 (although the difference was only statistically and/or clinically significant for a few dimensions). [redacted]

Across all cycles, [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs). Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm than the SoC arm [redacted]. Across all cycles, Grade ≥3 TEAEs were reported by [redacted] patients in the inotuzumab group and [redacted] patients in the SOC group. Most Grade ≥3 TEAEs were more frequent in the SoC arm than the inotuzumab arm, again with the exception of VOD; [redacted]

A total of [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group discontinued treatment due to adverse events. A further [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group had temporary discontinuations due to adverse events.

The CS presented supporting evidence from two non-RCT studies; study NCT01363297 and the MDACC study. The results were not as favourable in these studies as in the INO-VATE 1022 trial. However, both studies included patients who received inotuzumab as Salvage 3 or later therapy, therefore, patients in these studies had a poorer prognosis than those in the INO-VATE 1022 trial.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS described a systematic review of comparative studies of patients aged 15 or over with R/R ALL receiving a range of pharmacological treatments compared with another of the treatments listed, placebo or best supportive care. However, the CS stated that the criteria used in the systematic review were broader than those required for the submission; therefore, only studies specifically of interest to the NICE scope would be included. The specific eligibility criteria for inclusion in the submission were not stated, therefore, cannot be checked for appropriateness.

The search strategies were generally appropriate, although a secondary publication of one of the studies included as non-RCT evidence, appears to have been missed by the searches. However, it is unlikely that any relevant RCTs of inotuzumab have been missed.

The methods of the INO-VATE 1022 trial were described in adequate detail and the quality of the trial was assessed using appropriate criteria; the trial was reasonably good quality. However, some of the results were not presented in sufficient detail; the ERG requested additional data from the Company, which were provided. Data presented for the two non-RCT studies were limited and the results of the quality assessment were not presented.

The results of the INO-VATE 1022 trial relating to CR/CRi are likely to be reliable; whilst remission outcomes were assessed by unblinded study personnel, the results for the full ITT population were similar to those of the smaller ITT218 population, whose remission outcomes were assessed by an independent Endpoint Adjudication Committee (EAC).

The results relating to the higher proportion of inotuzumab patients proceeding to HSCT are also likely to be reliable, although [redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice, where patients have to have achieved CR/CRi to be eligible for HSCT. The economic model grouped all HSCT patients together, regardless of CR/CRi status. In addition [redacted] inotuzumab patients and [redacted] SoC patients did not receive HSCT, despite achieving CR/CRi; the ERG's clinical advisor stated that the decision to perform HSCT is complex; this complexity reflects the need to use hard clinically meaningful endpoints, such as overall survival.

The OS data were subject to some limitations. [redacted] The RMST analysis results presented in the CS were those for the truncation time of 37.7 months. The median OS presented for the SoC group was considerably higher than other estimates of OS, presented in Table 6 of the CS (range 3 to 5 months), suggesting that the RMST analysis appears to inflate OS.

Limitations in reporting patient-reported outcomes, in terms of the number of patients who completed questionnaires after treatment and the lack of reporting of actual quality of life scores, mean that these results should be interpreted with caution. The open label nature of the trial introduces potential bias for subjective endpoints.

The supporting evidence from two non-RCT studies was much less robust than the INO-VATE 1022 trial, both studies were small, did not include a non-inotuzumab control group and a proportion of patients did not receive inotuzumab at the recommended dosing schedule.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life, resource use and costs associated with inotuzumab and the treatment of R/R B cell ALL. The review did not identify any relevant cost effectiveness analyses.

The cost effectiveness of inotuzumab was informed by an economic evaluation conducted by the company. The company presented an economic model in the form of a decision tree combined with a partitioned survival approach, with an assumption that patients surviving three years after receipt of HSCT would in effect be cured. The model structure split the patient population into three sub populations: (i) No CR/CRi and no HSCT; (ii) CR/CRi and no HSCT; (iii) HSCT and post HSCT. Within each of these sub populations parametric survival models that included treatment as a covariate were used to divide patients according to whether they were progression-free, post progression or dead. The efficacy, 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. The company included the total number of 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 ([redacted] patients in the inotuzumab group and [redacted] in SoC). A discount rate of 1.5% per annum was applied to both costs and outcomes in the company base case, which the company justified based on the assumption that HSCT can restore patients to normal life expectancy. In response to clarification questions the company provided additional data and analyses from INO-VATE 1022 trial population and an updated economic model.

The company found inotuzumab to be more costly (cost difference of [redacted]) and more effective ([redacted] QALY gain) compared with standard of care using a discount rate of 1.5% for costs and outcomes. The deterministic base case ICER was £40,013, and the mean probabilistic ICER was £48,459. Using a discount rate of 3.5% on costs and health outcomes, the deterministic base case ICER was £55,869 per QALY, and the mean probabilistic ICER £67,575 per QALY. The majority of the QALY gain was conferred within the *HSCT & Post HSCT* sub population. The company reported that the most influential parameters in one way sensitivity analysis included the cost of stem cell transplantation, the cost and usage of blinatumomab as an induction therapy subsequent to standard of care, the utility values associated with progressed disease and the utility values assigned more than five years after HSCT.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

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

While the company discuss the cost-effectiveness of inotuzumab in terms of its role as a bridge to potentially curative treatment, such as HSCT, through increasing rates of remission, the ERG noted that there was no structural link in the company model between remission outcomes and HSCT. The lack of structural link prevented subgroup analysis around patient characteristics that can influence the rate of HSCT.

The ERG felt that splitting the INO-VATE 1022 trial into three sub populations and fitting multiple parametric survival models that incorporated treatment effects both on the shape and the scale of the hazard was overly complex. In particular, the parametric models fit to the *HSCT & Post HSCT* sub population in the company base case did not provide a suitable basis for extrapolation. The predictions from these models lacked external validity, and the imposition of a cure point at three years was required to prevent clinically implausible estimates for the standard of care comparator. There is a lack of robust support in the existing data for the company base case assumption of

additional survival benefit from inotuzumab after receipt of HSCT. The company submission included an exploratory analysis in which post HSCT survival was informed by MRD status. 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 company made significant effort to source relevant estimates of health related quality of life. However, there was some inconsistency between the cure assumption and the choice of utility values applied to long-term survival post HSCT. 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 resource use required for administration of inotuzumab and standard chemotherapy appeared to be underestimated in the company model. The company based the amount of blinatumomab and inotuzumab used as post-induction therapies on the ITT population, and applied the list price for both treatments in the base case model. The ERG felt that the inclusion of these costs was potentially inappropriate and that it was unclear whether the benefits from post-induction therapies were adequately reflected in the safety population used to inform the economic model.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The evidence presented for the clinical effectiveness of inotuzumab was primarily based on a reasonably good quality RCT. The effectiveness of inotuzumab was compared against FLAG-based chemotherapy in most patients, and the outcomes assessed were appropriate. The company's economic submission met the requirements of the NICE reference case. The company submission acknowledged many of the key uncertainties and the cost-effectiveness model incorporated a range of scenario analyses that allowed the impact of alternative assumptions to be explored.

1.6.2 Weaknesses and areas of uncertainty

The RCT of inotuzumab only included the subset of patients who were suitable for intensive therapy and were due to receive either Salvage 1 or Salvage 2 therapy, which is a subset of the anticipated licensed population. No comparative evidence has been presented for the use of inotuzumab in patients who require third or later salvage treatment, or who are not fit for intensive treatment or may be treated with palliative intent.

Two of the comparator treatments used in the RCT are not used in current NHS practice, whereas two treatments that are used in NHS practice were not used as comparators within the trial.

The main area of uncertainty in the cost-effectiveness analysis is whether inotuzumab leads to additional survival gains in patients after they have received HSCT, and there is limited, weak evidence to inform this assumption. There is further uncertainty as to the long-term health-related quality of life of patients following HSCT.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG adjusted the company model to make direct use of the Kaplan-Meier data from INO-VATE 1022 in place of parametric models. The ERG calculated administration costs that reflected the proportion of inotuzumab cycles delivered in an inpatient setting in INO-VATE 1022, and assumed a longer length of stay. The ERG identified studies to inform the increased risk of mortality among individuals who have received HSCT compared to the general population.

The ERG base case included the cost of therapies that were received in INO-VATE 1022 in order to maintain consistency with the efficacy data that inform the economic model. Sensitivity analysis was used to determine the costs if the standard of care group received FLAG-IDA as per current NHS practice. It was unclear whether the benefits of blinatumomab or inotuzumab as post-induction therapies were captured in the safety population, and so the scenario was applied which replaced these costs with those for standard chemotherapy. The ERG base case utilised an age adjustment to health-related quality of life utilities, and pooled on treatment utilities from INO-VATE 1022. The ERG non-parametric base case reflected the impact of inotuzumab on increasing remission and rate of HSCT, but assumed no additional survival gains post HSCT. An alternative ERG parametric base case incorporated additional survival gains post HSCT through the impact of inotuzumab on increasing the rate of MRD-negativity, and the prognostic value of MRD status estimated in the INO-VATE 1022 *HSCT & Post HSCT* safety sub population.

The ERG found inotuzumab to be more costly (cost difference [redacted] and more effective ([redacted] QALY gain) compared with standard of care using a discount rate of 3.5% for costs and outcomes. The ERG non-parametric base case ICER was estimated to be £122,174 per QALY gained for inotuzumab compared to standard of care, using a discount rate of 3.5%, and £97,988 per QALY using a discount rate of 1.5%. The ERG parametric base case ICER was £114,078 per QALY with a discount rate of 3.5% and £90,982 per QALY using a discount rate of 1.5%. This is higher than the company base case ICER, primarily because of the alternative assumptions about the post HSCT survival benefit of inotuzumab. It is also affected by the assumption that patients who survive HSCT continue to experience a fourfold increased risk of mortality compared to the general population.

Sensitivity analyses showed that alternative assumptions for costs and resource use were less influential on the ICER compared to assumptions about post HSCT survival.

2 Background

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem was appropriate and relevant to the decision problem under consideration. 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 a rare disease in adults, who account for only around 40% of ALL cases, but about 80% of ALL deaths. Around three quarters of ALL patients have disease derived from precursor B-cells (B-cell ALL), although there is some inconsistency within the company submission (CS), with figures of 75% and 82% reported, for the proportion of ALL patients whose disease is derived from precursor B-cells. B-cell ALL is further classified by Philadelphia chromosome (Ph) status; the majority of adults under the age of 60 with B-cell ALL have Ph negative (Ph-) disease. Ph positive (Ph+) disease is associated with poorer outcomes.

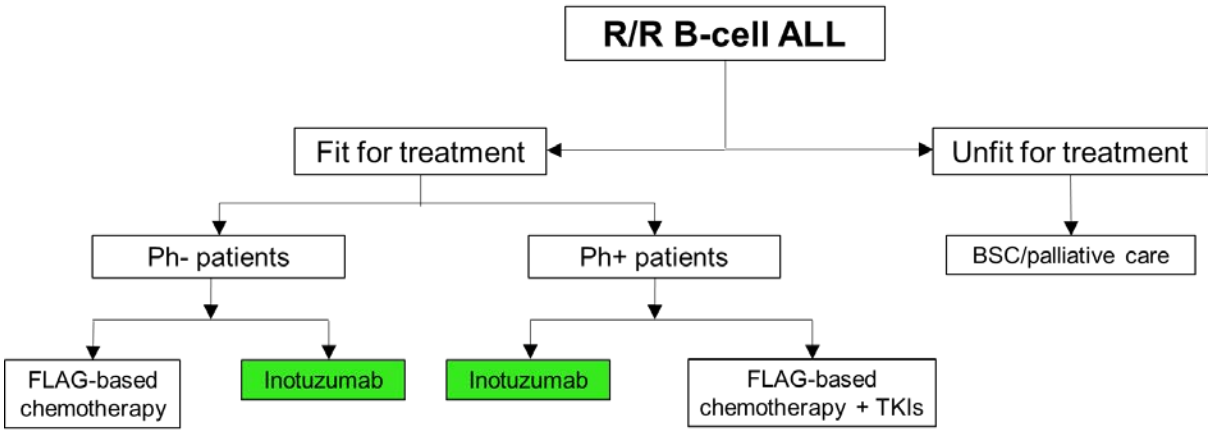
The CS stated that approximately 44% of adults with B-cell ALL are expected to relapse, and a further 4% are found to be treatment refractory. The only potentially curative treatment option is haematopoietic stem cell transplant (HSCT), although this is only available to patients who achieve a complete remission (CR) or complete remission with incomplete count recovery (CRi) to chemotherapy-based regimens and for whom a suitable donor can be found. Prognosis for relapsed or refractory (R/R) B-cell ALL is poor, with 5-year overall survival (OS) estimated to be less than 10%. The CS reported that survival following relapse may be as low as three months with current salvage therapies, which have low rates of CR/CRi and, therefore, few patients (5-30%) progress to further potentially curative therapies, whilst survival for patients who receive HSCT is over fourteen months. Survival rates are higher in patients who achieve CR/CRi at first salvage than patients who achieve CR/CRi at second or later salvage. A recently published international reference analysis of outcomes in adults with R/R Ph-negative ALL reported survival data based on 1,706 patients (including 1,416 patients with information on HSCT status).[2] Overall survival at 36-months was reported to be 11% in the overall population (including patients who did and did not receive HSCT) and exceeded 20% in patients who received HSCT following first salvage treatment.

The CS reported that the incidence of B-cell ALL is approximately 1.2 per 100,000 population, based on statistics provided by Cancer Research UK. The population of interest in the CS is adult patients with R/R B-cell ALL. It was estimated that the R/R B-cell ALL population for 2017 in England would be 117 patients. These figures appear reasonable.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision was generally appropriate and relevant to the decision problem under consideration. It correctly stated that there are currently no clinical guidelines from NICE relevant to the specific population of R/R B-cell ALL patients. Current treatment options are limited and include chemotherapy-based regimens for patients who are fit for treatment and palliative care for those who are unfit for intensive treatment. The aim of chemotherapy-based treatment is to achieve CR or CRi, which are eligibility requirements for future potentially curative therapies, such as HSCT. The CS stated that inotuzumab is suitable as a bridge to potentially curative therapy; therefore, it would be unsuitable for patients who are unfit for intensive treatment and would be treated with palliative intent. In the company's response to the ERG's Points for Clarification document, the company stated that in the proposed draft label, inotuzumab ozogamicin is not only intended for use in patients who can tolerate chemotherapy or proceed to potentially curative therapy (e.g. HSCT). However, patients being treated with palliative intent (e.g. patients receiving steroids, pain control, etc.) would not be expected to receive inotuzumab ozogamicin in NHS practice.

Figure 5 of the CS presented the current treatment pathway with the proposed placement of inotuzumab, this is presented below as Figure 1. This treatment pathway appears generally appropriate for Ph- patients, although clofarabine, which is available via the Cancer Drugs Fund (CDF), was not included. Clinical advice received by the Evidence Review Group (ERG) was that clofarabine is used in UK clinical practice, as an alternative to FLAG-based chemotherapy, and is efficacious. The NICE website states that a commissioning decision on clofarabine would be best taken by the CDF 'off label process' feeding into the NHS England Specialised Commissioning Policy Development prioritisation process. CDF transition funding will remain in place until a commissioning decision is taken by the CDF 'off label process'.[3] However, the ERG's clinical advisor did not agree with the treatment pathway presented for Ph+ patients; those relapsing post-HSCT might be treated with TKIs alone.



Key: ALL, acute lymphoblastic leukaemia; BSC, best supportive care; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; Ph-, Philadelphia chromosome negative; Ph+ Philadelphia chromosome positive; R/R, relapsed or refractory; TKI, tyrosine kinase inhibitor.

Figure 1: Current treatment pathway with proposed placement of Inotuzumab

A new report by NHS England 'Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages)' states that NHS England will routinely commission the use of second allogeneic HSCT for relapsed disease for patients meeting specific criteria (see report for further details).[4] Therefore, the proposed use of inotuzumab, as a bridge to potentially curative therapy, is now extended to patients who have received a previous HSCT, where previously such patients would not have been eligible for second HSCT.

3 Critique of company's definition of decision problem

3.1 Population

The population in the CS matched that specified in the NICE scope: adults with relapsed or refractory B-cell acute lymphoblastic leukaemia. However, the CS stated that "inotuzumab is suitable as a bridge to potentially curative therapy (usually HSCT), patients who are unfit for intensive therapy, such as chemotherapy-based treatments, will also be unfit for transplantation. Therefore, inotuzumab would also be unsuitable for these patients". Consequently, only a subset of adults with R/R B-cell ALL would be suitable for inotuzumab in clinical practice; those who are fit for intensive therapy, such as chemotherapy-based treatments and transplantation. The anticipated licenced population, defined in the draft Summary of Product Characteristics, is the broader population of "[redacted]".

The clinical effectiveness evidence presented is primarily from a randomised controlled trial (RCT), the INO-VATE 1022 trial, in which the population comprised only the subset of patients who were

suitable for intensive therapy: "relapsed or refractory CD22-positive ALL due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option"; therefore patients who would be treated with palliative intent were not eligible for the trial.[2] The restriction on the number of prior salvage treatments within the trial population means that patients in the trial had a better chance of response than patients who have already received two or more salvage therapies; these patients are less likely to respond to any further therapy. The ERG clinical advisor stated that the INO-VATE 1022 trial is broadly applicable to patients seen in NHS practice, although it is unclear what previous chemotherapy regimens the patients had relapsed on, and whether these previous regimens are relevant to UK practice.

The CS also included two non-RCT studies of inotuzumab in adults with R/R B-cell ALL as supporting evidence.[5, 6] Study NCT01363297 was a single-arm US study which comprised a dose finding study and a dose-expansion study.[6] The MD Anderson Cancer Center (MDACC) study was a US observational study of patients with R/R B-cell ALL, from which data for 75 adult patients treated with inotuzumab were presented in the CS.[5] Both of these studies included a proportion of patients who received inotuzumab as Salvage 3 or later therapy (38% of patients in the NCT01363297 study and 30% of patients in the MDACC study) in addition to those who received inotuzumab as Salvage 1 or Salvage 2; therefore, these patients had a poorer prognosis than those in the INO-VATE 1022 trial.

3.2 Intervention

The intervention in the CS matched that specified in the NICE scope: inotuzumab ozogamicin. Inotuzumab is currently awaiting marketing authorisation, [redacted]. It was granted orphan designation by the European Commission on 7th June 2013. Inotuzumab is administered intravenously, by infusion over one hour, at a starting dose of 1.8 mg/m^2 (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15). Cycle 1 lasts for 21 days, but may be extended to 28 days if the patient achieves CR/CRi and/or to allow recovery from toxicity. Each subsequent cycle lasts for 28 days. Once a patient reaches CR/CRi the starting dose on Day 1 of the cycle is reduced to 0.5 mg/m^2 for the duration of treatment. [redacted] In the INO-VATE 1022 trial, patients received inotuzumab at the recommended dose, for up to six treatment cycles (median 3.0 cycles).

The CS highlighted the more convenient administration schedule for inotuzumab, in comparison with fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based chemotherapy. The CS stated that inotuzumab can be administered in the outpatient setting, reducing resource use. However, clinical advice received by the ERG was that the first cycle of inotuzumab is likely to be administered as an inpatient, as similar monitoring is required as for FLAG-based chemotherapy. The first cycle is a higher risk procedure, with suppression of bone marrow. Subsequent cycles of inotuzumab, when healthy bone marrow has regenerated, could be done on an outpatient basis. The ERG requested further information from the company on the number of patients who were treated with inotuzumab on an inpatient basis, rather than outpatient basis, by treatment cycle. The Company stated that [redacted].

3.3 Comparators

The NICE scope listed comparators for people who are able to take chemotherapy and have Ph- ALL as "fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy or clofarabine-based combination chemotherapy (not appraised by NICE but funded via the CDF)". However, clofarabine was not considered as a comparator in the submission, with the justification being that it "is licenced in R/R B-cell ALL for patients up to the age of 21, and only for patients receiving second treatment following relapse or failure to respond to induction therapy (that is, "second salvage")." The company stated that "as this appraisal is for the adult population, clofarabine represents an off-label comparator and is thus not deemed appropriate to compare to inotuzumab within the submission…" As stated in Section 2.2, clinical advice received by the ERG was that clofarabine is used in UK clinical practice and is efficacious, therefore, should have been a comparator in the submission.

The NICE scope listed comparators for people who are able to take chemotherapy and have Ph+ ALL as "tyrosine kinase inhibitors (TKIs) alone or in combination with FLAG- or clofarabine-based chemotherapy". However, TKIs alone (as well as TKIs in combination with clofarabine-based chemotherapy) were not considered as a comparator in the submission, with the justification being that "TKIs are commonly used alongside chemotherapy-based regimens in Ph+ patients in UK clinical

practice, however there is unlikely the use of TKIs *alone* in the R/R B-cell ALL population would occur. TKIs are hence included in addition to FLAG-based chemotherapy for Ph+ patients in the economic evaluation, but not alone". Clinical advice received by the ERG was that TKIs alone should have been a comparator in the submission, as TKIs are important for Ph+ patients and are often used alone as salvage therapy post-HSCT.

Blinatumomab has been investigated for adult patients with relapsed or refractory Ph- B-cell ALL in an open label RCT (the TOWER trial), however, it is in the process of being appraised by NICE and is not current standard of care, therefore, it was appropriate that it was not included as a comparator at this time.[8]

The NICE scope also included a "best supportive care (including palliative care)" comparator, for people who are unable to take chemotherapy. However, this was removed from the list of comparators as "treatment with inotuzumab acts as a bridge to reaching potentially curative therapy. Therefore, a comparison to best-supportive care or palliative care is not considered appropriate." As stated in Section 3.1, only a subset of adults with R/R B-cell ALL would be suitable for intensive therapy in practice, therefore, patients who would be treated with palliative intent are not represented in the CS, despite the population stated in the decision problem and those defined in the draft Summary of Product Characteristics being the broader population of "[redacted]".

The comparator used in the INO-VATE 1022 trial was the investigator's choice of one of the following three regimens: FLAG for up to four 28-day cycles (n=102), cytarabine plus mitoxantrone (CM) for up to four 15-20-day cycles (n=38) and high dose cytarabine (HIDAC) for up to one 12-dose cycle (n=22). Neither CM nor HIDAC were listed in the NICE scope, as these two treatments are not used in current NHS practice. Neither of the non-randomised studies included a non-inotuzumab control group.

3.4 Outcomes

The outcomes listed in the NICE scope were reported in the CS; overall survival, progression-free survival, treatment response rates (including haematologic responses), time to and duration of response, adverse effects of treatment and health-related quality of life. Two new outcomes were added to those listed in the NICE scope: minimal residual disease negativity (MRD-) and rate of potentially curative therapy, such as HSCT. Both of the additional outcomes appear to be appropriate, they are surrogate outcomes associated with improved patient survival after potentially curative therapy. However, the clinical expert statement submitted by Professor Adele Fielding emphasised

that "the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED", therefore, the results relating to MRD negativity should be interpreted with caution, particularly for patients receiving second salvage treatment, for whom MRD negativity has not been shown to be associated with better survival outcomes.[1]

The two primary outcomes of the INO-VATE 1022 trial were CR/CRi and OS. At an advisory board meeting, organised by Pfizer UK and BresMed, clinicians broadly agreed that the benefit of inotuzumab is the increase in CR/CRi and that the value of inotuzumab was therefore to act as a bridge to HSCT. The clinicians noted that, whilst the OS benefit from inotuzumab would be the focus of the appraisal, the available data are far less convincing than CR/CRi rates and the benefit seen in progression-free survival (PFS).[9]

3.5 Other relevant factors

The CS stated that no equality issues related to the use of inotuzumab have been identified or are foreseen.

4 Clinical Effectiveness

This section contains a critique of the methods of the systematic review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies. The ERG's conclusions on the clinical effectiveness of inotuzumab for treating adult R/R B-cell ALL are presented at the end of this section.

4.1 Critique of the methods of review

4.1.1 Searches

The CS described the search strategies used to identify relevant comparative studies of specified interventions used in the treatment of R/R B-cell ALL. The search strategies were briefly described in the main body of the submission and full details were provided in Appendix 2.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the Cochrane Central Register of Controlled Trials [CENTRAL] and the Health Technology Assessment Database [HTAD]) were searched on 27 September 2016. The search strings used for each database were reported in Appendix 2 of the CS.

The basic structure of the search strategies for MEDLINE, MEDLINE In Process, EMBASE and the Cochrane Library were appropriate. Terms for R/R B-cell ALL were combined with terms for inotuzumab or other relevant drugs used to treat R/R B-cell ALL from the NICE scope (blinatumomab, clofarabine, dasatinib, imatinib, ponatinib, FLAG, FLAG-HAD, HIDAC). The MEDLINE In Process search strategy did not include the drug terms, so would have retrieved studies of any interventions for R/R B-cell ALL not yet in MEDLINE, which is appropriate. The strategies contained relevant subject headings, text word searches and synonyms for R/R B-cell ALL, inotuzumab and the other drugs included in the strategy. A possible typing error was identified in the search strategies: lympholeuci* would have been more appropriately truncated as lympholeuc*. In the search of MEDLINE In Process a lack of truncation was noted which would have affected the sensitivity of this search, however truncation was used appropriately in the other databases searched.

No date limits were applied to the database searches. The company clarified that a limit to English language studies was applied to the searches of MEDLINE and EMBASE. Study design search filters were applied to the strategies for MEDLINE and EMBASE to limit retrieval to RCTs or non-RCTs. The company clarified that the source of the search filters was Scottish Intercollegiate Guidelines

Network (SIGN). The SIGN RCT filter and the SIGN observational studies filter included in the search strategies were developed in-house at SIGN rather than undergoing more formal development and validation. As the purpose of the search was to retrieve randomised as well as non-randomised studies, the sensitivity of the search could have been improved by removal of the SIGN study design search filters. An alternative approach would have been to use study design search filters which have undergone more thorough development and testing and have published performance data available.

The company attempted to remove literature reviews, whilst keeping systematic reviews or meta-analyses, from the searches of MEDLINE and EMBASE (line 38, page 8, Appendix 2). As a limited number of search terms for reviews, systematic reviews and meta-analyses were used at line 38, the strategy could have inadvertently removed systematic reviews and meta-analyses from the search results. Systematic reviews and meta-analyses prior to the 2015, would have been identified through their searches of the DARE database. However as DARE closed in March 2015 any published after this date would need to be identified through MEDLINE and EMBASE. A more appropriate method would have been to leave line 38 out of the strategy and exclude these literature reviews at the screening stage.

The company clarified that trial registers were not searched for the clinical effectiveness review, therefore it is possible that relevant ongoing studies would not have been identified by the searches presented. The ERG carried out a search of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register on 22nd March 2017 and identified 98 records (unduplicated) relating to ongoing studies of inozotumab. Ongoing studies of inotuzumab in patients with leukaemia are listed in Section 4.1.7.

The methods used to search for studies via conference proceedings and websites were not presented in the submission. However, the conference proceedings sources and websites searched were appropriate.

The search issues reported above may have potentially reduced the effectiveness of the searches in identifying all relevant studies for the clinical effectiveness review. The electronic searches appear to have missed a publication by Kantarjian et al. in 2012; this publication presented the results of part 1 of the NCT01363297 study that was included in the CS as supporting evidence.[10] It is unclear why this study was not identified by the searches, as it was published in Lancet Oncology, which is indexed in both MEDLINE and EMBASE. However, it is unlikely that any relevant RCTs of inotuzumab have been missed.

4.1.2 Inclusion criteria

The inclusion criteria for the systematic review were quite broad; comparative studies of patients aged 15 or over with relapsed or refractory ALL receiving a range of pharmacological treatments (including inotuzumab, blinatumomab, dasatinib, imatinib, ponatinib, clofarabine, FLAG, FLAG-IDA, HIDAC, Ara-C plus mitoxantrone, amongst others) compared with another of the treatments listed, placebo or best supportive care. However, the CS stated that the criteria used in the systematic review were broader than those required for the submission, therefore, only studies specifically of interest to the NICE scope would be included.

In the company's response to the ERG's Points for Clarification document, the company stated that the systematic review had wider objectives than those specifically required for the submission, in order to capture the potential relevant comparators ahead of the NICE scoping meeting.

The eligibility criteria for inclusion in the submission were not stated, therefore, cannot be checked for appropriateness. It appears that studies of patients with R/R B-cell ALL receiving inotuzumab were eligible for inclusion in the submission. One of the non-RCT studies included in the submission as supporting evidence was a single-arm study, despite this study design meeting the systematic review exclusion criteria of 'single arm studies'.

The inclusion/exclusion criteria for the review stated that studies would not be excluded on the basis of publication language; however, in the PRISMA flow diagram on page 68 of the CS, it stated that two studies were excluded for being non-English. In the company's response to the ERG's Points for Clarification document, the company stated that the objective of the review was to include studies published in English language only and that there was no intent to extract any data from non-English studies. Despite this inconsistency, it is unlikely that any relevant studies of inotuzumab were excluded from the submission on the basis of language of publication. The clinical study reports for the INO-VATE 1022 trial and study NCT01363297 were presented in the PRISMA flow diagram as 'additional sources for submission', rather than identified by the searches.

The CS stated that two reviewers independently screened studies for inclusion in the review, with discrepancies resolved through discussion or involvement of a third reviewer, reducing the risk of error and bias in study selection. However, it was not reported whether the same method was used for selecting the inotuzumab-specific studies for inclusion in the submission.

4.1.3 Data extraction

The CS stated that data were extracted from included studies by one reviewer and all extracted data checked by a second reviewer, with queries resolved through discussion and/or involvement of a third reviewer. This was appropriate, reducing the risk of error and bias in data extraction.

Adequate data from the INO-VATE 1022 trial were presented in the CS, with a detailed summary of the trial methods presented as Table 11 (pages 72-78 of the CS). The non-RCT studies presented as supporting evidence were described briefly in the CS, with limited details of the methods, participant characteristics and results.

4.1.4 Quality assessment

The INO-VATE 1022 trial was assessed for quality using appropriate criteria specific to RCTs; the trial was reasonably good quality (see Section 4.2.2 for further details). A table of quality assessment results was presented on page 90 of the CS, which was checked by the ERG.

The CS stated that non-RCT studies were assessed using the Downs and Black checklist. However, quality assessment results for the non-RCT studies were not presented in the CS.

4.1.5 Evidence synthesis

The results of the individual studies were presented separately, which was appropriate in view of the differences in study design and participant characteristics.

4.1.6 Conclusions from the critique of systematic review methods

The search strategy was generally appropriate, it is unlikely that any relevant RCTs of inotuzumab have been missed. Whilst inclusion/exclusion criteria were clearly stated for the systematic review, these were not the same as those applied when selecting studies for the submission. The eligibility criteria for the submission were not stated so cannot be checked for appropriateness. Data extraction and quality assessment appear to have been undertaken by one reviewer and independently checked by a second reviewer, reducing the risk of error and bias. Adequate details of the methods of the INO-VATE 1022 trial were presented, along with results of the quality assessment; the trial was reasonably good quality. However, details of the non-RCT studies presented as supporting evidence were limited and the results of the quality assessment of these studies were not reported in the CS.

4.1.7 Ongoing studies

The CS did not report any ongoing studies of inotuzumab, other than to state that no further studies will provide additional evidence for the indication being appraised within the next 12 months. The ERG identified the following ongoing studies of inotuzumab in patients with leukaemia:

- Phase I/II Study of Bosutinib in Combination With Inotuzumab Ozogamicin in CD22-positive Philadelphia-Chromosome (PC) Positive Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML). ClinicalTrials.gov Identifier: NCT02311998. Status: currently recruiting participants.
- CMC-544 and Allogeneic Transplantation for CD22 Positive-Lymphoid Malignancies. ClinicalTrials.gov Identifier: NCT01664910. Status: currently recruiting participants.
- Inotuzumab Ozogamicin in Treating Younger Patients With Relapsed or Refractory CD22 Positive B Acute Lymphoblastic Leukemia. ClinicalTrials.gov Identifier: NCT02981628. Status: not yet open for participant recruitment.
- S1312, Inotuzumab Ozogamicin and Combination Chemotherapy in Treating Patients With Relapsed or Refractory Acute Leukemia. ClinicalTrials.gov Identifier: NCT01925131. Status: currently recruiting participants.
- Study of the Combination of Inotuzumab Ozogamycin (CMC-544) With Low-intensity Chemotherapy in Patients With Acute Lymphoblastic Leukemia (ALL). ClinicalTrials.gov Identifier: NCT01371630. Status: currently recruiting participants.
- The safety and efficacy of the medicine Inotuzumab Ozogamicin in children with relapsed/refractory acute lymphatic leukemia (ALL). ID: EUCTR2016-000227-71-NL. Status: authorised-recruitment may be ongoing or finished.

The ERG also identified a number of studies of inotuzumab in patients with lymphoma.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Trials included in the review

One RCT was included in the submission; the INO-VATE 1022 trial, which compared inotuzumab to standard of care (SoC), which was the investigator's choice of FLAG, CM or HIDAC.[2] The INO-VATE 1022 trial was an international multicentre open-label parallel-group RCT, including eight sites in the UK. However, only nine patients (4 in the inotuzumab arm and 5 in the SoC arm) were included in the trial from the eight UK centres (reported on page 143 of the CS). Adult patients (aged 18 or over) with R/R CD22-positive B-cell ALL due to receive their first or second salvage therapy, and for whom either arm of the trial offered a reasonable treatment option, were randomised in a 1:1

ratio to either inotuzumab or SoC. Patients with Ph+ disease were also required to have failed treatment with at least one second- or third-generation TKI, which the CS states is in line with current NHS practice.

A summary of the methods of the INO-VATE 1022 trial, including trial design, eligibility criteria, interventions and outcomes of interest, are presented in Table 1 (Table 11 of the CS).

Table 1: Summary of INO-VATE 1022 methodology

Study	**INO-VATE 1022**
Location	The study was initiated at 193 centres in Argentina, Australia, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Finland, France, Germany, Hungary, Italy, Japan, Republic of Korea, Netherlands, Poland, Serbia, Singapore, Slovakia, Spain, Sweden, Taiwan, UK (8 sites), and the US. Of these, 129 centres screened or treated at least 1 patient.
Trial design	Phase III, randomised, multicentre, global, open-label, two-group trial. Randomisation was stratified by duration of first remission (<12 months vs ≥12 months), salvage-treatment phase (first vs second) and age (<55 vs ≥55).
Eligibility criteria for participants	**Inclusion criteria were:** • Relapsed or refractory CD22-positive ALL (≥5% marrow blasts, assessed by morphology; i.e. M2 or M3 marrow) due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option • Patients with Ph+ ALL must have failed treatment with at least 1 second- or third-generation TKI and standard multi-agent induction chemotherapy • Patients in Salvage 1 with late relapse deemed poor candidates for reinduction with initial therapy • Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment • Aged 18 years or older • Eastern Cooperative Oncology Group (ECOG) performance status 0–2 • Adequate liver function, including total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless the patient had documented Gilbert syndrome, and AST and ALT ≤2.5 × ULN. If organ function abnormalities were considered due to tumour, total serum bilirubin had to be ≤2 × ULN and AST/ALT ≤2.5 × ULN • Serum creatinine ≤1.5 × ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 ml/minute • Male and female patients of childbearing potential and at risk for pregnancy had to agree to use a highly effective method of contraception throughout the study and for a minimum of 90 days after the last dose of assigned treatment. A patient was of childbearing potential if, in the opinion of the Investigator, he/she was biologically capable of having children and was sexually active. Female patients who were not of childbearing potential (i.e. met at least 1 of the following criteria):

Study	INO-VATE 1022
	○ Had undergone hysterectomy or bilateral oophorectomy; or ○ Had medically confirmed ovarian failure; or ○ Were medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause) • Evidence of a personally signed and dated Informed Consent Document (ICD) indicating that the patient had been informed of all pertinent aspects of the study; patients with mental capacity that required the presence of a legally authorised representative were excluded from the study • Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures **Exclusion criteria were:** • Isolated extramedullary relapse (i.e. testicular or CNS) • Burkitt's or mixed phenotype acute leukaemia based on the World Health Organization (WHO) 2008 criteria • Active CNS leukaemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid, use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukaemia (i.e. cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication was not a reason for exclusion • Prior chemotherapy within 2 weeks before randomisation with the following exceptions: ○ To reduce the circulating lymphoblast count or palliation: i.e. steroids, hydroxyurea or vincristine ○ For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or TKIs • Patients must have recovered from acute non-haematologic toxicity (to ≤Grade 1) of all previous therapy prior to enrolment • Prior monoclonal antibodies within 6 weeks of randomisation, with the exception of rituximab that must have been discontinued at least 2 weeks prior to randomisation • Prior allogeneic HSCT or other anti-CD22 immunotherapy ≤4 months before randomisation. Patients must have completed immunosuppression therapy for treatment of graft versus host disease (GvHD) prior to enrolment. At randomisation, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD • Peripheral absolute lymphoblast count ≥10,000/μL (treatment with hydroxyurea and/or steroids/vincristine was permitted within 2 weeks of randomisation to reduce the white blood cell [WBC] count) • Known systemic vasculitides (e.g. Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as human immunodeficiency virus [HIV] infection or severe inflammatory disease)

Study	**INO-VATE 1022**
	• Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for HIV. HIV testing was performed in accordance with local regulations or local practice • Major surgery within ≤4 weeks before randomisation • Unstable or severe uncontrolled medical condition (e.g. unstable cardiac function or unstable pulmonary condition) • Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localised prostate cancer that had definitely been treated with radiation or surgery. Patients with previous malignancies were eligible provided that they had been disease-free for ≥2 years • Cardiac function, as measured by left ventricular ejection fraction (LVEF) that was less than 45%, or the presence of New York Heart Association (NYHA) Stage III or IV congestive heart failure • Patients with active heart disease (NYHA class ≥3 as assessed by history and physical examination) • QTcF >470 msec (based on the average of 3 consecutive ECGs) • Myocardial infarction ≤6 months before randomisation • History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of atrioventricular (AV) block unless a permanent pacemaker had been implanted • Uncontrolled electrolyte disorders that could have compounded the effects of a QT interval (corrected for heart rate [QTc]) prolonging drug (e.g. hypokalaemia, hypocalcaemia, hypomagnesemia) • History of chronic liver disease (e.g. cirrhosis) or suspected alcohol abuse • History of hepatic VOD • Administration of live vaccine ≤6 weeks before randomisation • Evidence of uncontrolled current serious active infection (including sepsis, bacteraemia, fungaemia) or patients with a recent history (within 4 months) of deep tissue infections such as fasciitis or osteomyelitis • Patients who had a severe allergic reaction or anaphylactic reaction to any humanised monoclonal antibodies • Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for a minimum of 90 days after the last dose of study drug (inotuzumab ozogamicin) • Patients who were investigational site staff members or relatives of those site staff members or patients who were Pfizer

Study	INO-VATE 1022
	employees directly involved in the conduct of the study • Participation in other studies involving investigational drug(s) (Phase I-IV) within 2 weeks from randomisation to EOT visit • Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration or may have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study
Settings and location where the data were collected	Project management, data management, clinical monitoring, site monitoring, data programming, and medical writing were performed by ICON plc. Biostatistical analyses were performed by ICON. This study used an external Data Monitoring Committee (eDMC), an external Hepatic Events Adjudication Board (HEAB) and an Endpoint Adjudication Committee (EAC).
Trial drugs	**InO:** Patients received inotuzumab at a starting dose of 1.8mg/m^2 per cycle (0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15). Cycle 1 lasted for 21 days, up to 28 days if necessary for toxicity recovery, and each subsequent cycle lasted for 28 days. Patients received treatment for up to 6 cycles. Once a patient achieved complete remission or complete remission with incomplete haematologic recovery, the Day 1 dose was reduced to 0.5mg/m^2 for the duration of the trial. **Standard-therapy:** Investigator's choice of one of the following 3 regimens: • FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor) therapy for up to four 28-day cycles (with cytarabine at a dose of 2.0g/m^2 per day on Days 1–6, fludarabine at a dose of 30mg/m^2 per day on Days 2–6, and granulocyte colony-stimulating factor at a dose of 5µg/kg per day or at the institutional standard dose) • Cytarabine plus mitoxantrone (CM) for up to four 15–20-day cycles (with cytarabine at a dose of 200mg/m^2 per day on Days 1–7 and mitoxantrone at a dose of 12mg/m^2 per day on Days 1–3; for mitoxantrone, dose reduction to 8mg was allowed based on age, coexisting conditions, and previous anthracycline use) • High dose cytarabine (HIDAC) for up to one 12-dose cycle (at a dose of 3g/m^2 every 12 hours, or a dose of 1.5g/m^2 for patients ≥55 years of age) Patients who achieved CR could undergo HSCT at the investigator's discretion. (However, some patients progressed to HSCT with CRi, and a small number of patients [8 vs 12 for inotuzumab vs SoC, respectively] received HSCT without either CR or CRi).
Permitted and disallowed concomitant	**Permitted concomitant medication:** • Any medication for a concurrent medical condition was permitted and was supplied by the study site. The use of hydroxyurea was permitted for temporary control of WBC elevations in patients with aggressive disease both prior to and during the first 5

Study	**INO-VATE 1022**
medication	days of study treatment. Reduction of peripheral blast counts to at least 10,000/µL was required for randomisation. If required, hydroxyurea was given at a dose of 1–5g daily for up to 5 days in Cycle 1. • Concurrent therapy for CNS prophylaxis/treatment (e.g. intrathecal methotrexate) was strongly encouraged. • Growth factors such as G-CSF, including pegfilgrastim, and granulocyte-macrophage-colony stimulating factor were allowed as supportive care with each cycle if clinically indicated after the last dose of study drug or chemotherapy in accordance with local guidelines and medical practice. • Corticosteroids were allowed for cytoreduction, CNS prophylaxis/treatment, as premedications for up to 1 day, to treat hypersensitivity reactions for up to 1 day, and as an antiemetic for up to 8 days/cycle as supportive care. Intranasal, inhaled, or topical corticosteroids (i.e. local administration rather than systemic delivery) were allowed, as were low doses of corticosteroids (≤10mg of prednisone or equivalent/day) throughout study participation. Higher doses of steroids were discouraged if alternative therapy was available. It was crucial to enter dosing details for systemic corticosteroids administered in the case report form due to their possible influence on the primary endpoint. **Prohibited concomitant medication:** • Craniospinal radiation therapy (CSXRT) was prohibited during study treatment. If CSXRT was clinically indicated, the patient was withdrawn from study therapy (i.e. EOT). • Anticancer therapy other than as defined/allowed in the protocol and other investigational agents were prohibited throughout the treatment period of the study. • Medications known to predispose patients to Torsades de pointes were prohibited throughout the treatment period of the study. If a medication known to predispose to Torsades de pointes was considered medically necessary to treat a life-threatening condition, the Sponsor was to be notified immediately, and additional ECGs may have been required prior to redosing with study drug. **Discouraged concomitant medication:** • Patients were strongly encouraged to avoid agents known to be strong cytochrome P450 (CYP) -inducing or -inhibiting agents for the duration of the treatment period of the study. However, these medications were permitted if clinically indicated and necessary. In addition, patients were strongly encouraged to avoid herbal supplements including, but not limited to, St. John's wort throughout the treatment period of the study. Note: Data not available at the time of the original protocol have indicated that multiple metabolic pathways are involved in the metabolism of unconjugated calicheamicin; and the use of CYP inducing or inhibiting agents is not considered to have a clinically meaningful impact on the pharmacokinetics of inotuzumab.

Study	**INO-VATE 1022**
Primary outcome	The two primary outcomes were: • Complete remission (CR), including complete remission with incomplete haematologic recovery (CRi) was assessed by the EAC at screening, Days 16–28 of Cycles 1, 2 and 3 and then every 1–2 cycles (or as clinically indicated) and at the final visit. Note that the cycle length could be extended from 21 to 28 days to allow for toxicity recovery, if necessary. o CR was defined as a disappearance of leukaemia as indicated by <5% marrow blasts and the absence of peripheral blood leukaemic blasts, with recovery of haematopoiesis defined by an absolut neutrophil count (ANC) ≥1000/µL, platelets ≥100,000/µL, and resolution of any extramedullary disease o CRi was defined as CR except with ANC <1000/µL and/or platelets <100,000/µL • Overall survival (OS), defined as the time from randomisation to the date of death due to any cause (patients for whom the date of death could not be verified were censored at the date of last contact). For the long-term follow-up, patients who discontinued treatment but had not relapsed were followed-up every 12 weeks in Year 1 and 24 weeks in Year 2 (and beyond) for disease assessment. After disease progression, patients were followed up every 12 weeks for survival. The trial is planned to end upon last patient enrolled having been followed for 2 years from randomisation.
RMST analysis of OS	Since the OS data in the study appeared to depart from the proportional hazards assumption, as reflected in the widened separation of the survival curves around 15 months from randomisation (See Section 4.7), an exploratory post-hoc analysis based on the RMST method was conducted. The RMST method is an alternative approach to estimate the treatment effect, especially when the assumption of proportional hazards is not satisfied. (Royston, 2011;Uno, 2014;Uno, 2015 #77) This method measures the average survival from time 0 to a specified time point (known as the 'truncation time'). As reported by Trinquart et al.(Trinquart, 2016), in general, RMST-based measures yield more conservative estimates than hazard ratios (HRs), with HRs providing, on average, larger treatment effect estimates than the ratio of RMST; and RMST-based measures should be routinely reported in randomised studies with time-to-event outcomes. The RMST method is discussed in more detail in Section 4.4.
Major secondary outcomes	Secondary endpoints included: • Progression-free survival (PFS), defined as the time from date of randomisation to the earliest date of the following events: death, progressive disease (objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status), or starting a new induction therapy or post-therapy HSCT without achieving CR/CRi • Minimal residual disease (MRD), defined as the percentage of patients, among those who achieved complete remission (as assessed by the EAC), who had results below the threshold for MRD; specified as 0.01% bone marrow blasts, was assessed by

Study	**INO-VATE 1022**
	a central laboratory • Duration of remission (CR and CRi), as assessed by the investigator • The rate of subsequent HSCT (patients who achieved response and found a suitable donor could receive HSCT at the investigator's discretion) For the long-term follow-up, patients who discontinued treatment but had not relapsed were followed-up for these outcomes every 12 weeks in Year 1 and 24 weeks in Year 2 for disease assessment. After disease progression, patients were followed up every 12 weeks for survival. • Patient-reported outcomes (assessed at day one of each cycle and at the end of treatment): o EORTC QLQ-C30 o EQ-5D
Other outcomes	• Safety • The relationship between efficacy and the percentage of CD22 positive leukaemic blasts • Pharmacokinetics and pharmacodynamics • Pharmacogenomics • Cytogenetics • Immunogenicity
Pre-planned subgroups	Pre-planned subgroups for analysis of CR/CRi included stratification factors: • Duration of first remission (<12 months or ≥12 months) • Salvage status (first or second) • Age at randomisation (<55 years or ≥55 years) Pre-planned subgroups for analysis of OS included: • Stratification factors (the same as for CR/CRi subgroup analysis) • By salvage status per CRF • By age per CRF (<55 years, ≥55 and <65 years or ≥65 years) • By cytogenetics per local laboratory: diploid (normal), Ph+, t(4;11), and complex

Study	**INO-VATE 1022**
	• By HSCT prior to enrolment: yes or no • By baseline marrow blast (%): <50% or ≥50% • By baseline peripheral blasts per local laboratory: 0/µL, >0–1000/µL or >1000/µL • By percentage of leukaemic blasts that were CD22-positive at baseline per central laboratory • By type of remission per EAC: CR or CRi in the ITT218 Population • By type of remission per Investigator's assessment: CR or CRi • By MRD status (central review): positive or negative • By post randomisation HSCT: yes or no • By region • By gender • By race • By body mass index (BMI) (<30, ≥30) Pre-planned subgroups for analysis of PFS included: • Stratification factors • Duration of first remission • Salvage status per CRF • Age per CRF (<55 years, ≥55 and <65 years or ≥65 years) • Cytogenetics per local laboratory: diploid (normal), Ph+, t(4;11), and complex
Key: ALL, acute lymphoblastic leukaemia; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CR, complete remission; CRF, case report form; CRi, complete remission with incomplete haematologic recovery; EAC, endpoint adjudication committee; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; EQ-5D, EuroQoL 5 Dimension questionnaire; G-CSF, granulocyte colony-stimulating factor; HSCT, haematopoietic stem cell transplantation; ICD, Informed Consent Document; InO, inotuzumab ozogamicin; ITT, intent-to-treat; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome positive; RMST, restricted mean survival time. **Source:** INO-VATE 1022 CSR[11]	

As discussed in Section 3.1, the population in the INO-VATE 1022 trial comprised only a subset of the anticipated licenced population: "relapsed or refractory CD22-positive ALL due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option". Therefore patients who were unable to tolerate intensive treatment were not eligible for the trial and the restriction on the number of prior salvage treatments within the trial population means that patients in the trial had a better chance of response than patients who have already received two or more salvage therapies. The ERG clinical advisor stated that the INO-VATE 1022 trial is broadly applicable to patients seen in NHS practice, although it is unclear what previous chemotherapy regimens the patients had relapsed on, and whether these previous regimens are relevant to UK practice.

Sixty-three percent of patients in the SoC arm received FLAG-based chemotherapy, 23% received CM and 14% received HIDAC. As discussed in Section 3.3, neither CM nor HIDAC are used in current NHS practice, whereas clofarabine and TKIs alone (for Ph+ patients) are used in clinical practice, but were not included as SoC in the trial.

The outcomes assessed in the trial were appropriate, although the RMST analysis was an exploratory post-hoc analysis.

The required sample size was calculated to allow adequate assessments of between group differences in remission and survival outcomes; a sample size of 218 patients was required to detect a significant difference in CR/CRi and at least 325 patients and 248 OS events were required to detect a significant difference in OS. A pre-specified analysis of CR/CRi was performed after the first 218 patients had been followed for at least three months after randomisation, with a cut-off date of 2 October 2014 (the ITT218 population). The last (326^{th}) patient was randomised to the study on 4 January 2015 and the 248^{th} OS event was reached on 8 March 2016; therefore, this date was selected as the cut-off date for OS and PFS analyses (ITT population). The safety population (also called the modified ITT (mITT) population) included all randomised patients who received at least one dose of study drug by 2 October 2014 (307 patients; 164 in the inotuzumab arm and 143 in the SoC arm). Participant baseline characteristics are summarised in Table 2, for both the ITT218 population and the full ITT population (Table 14 of the CS).

Table 2: Baseline characteristics of participants in the INO-VATE 1022 trial

	ITT218 population[a]		ITT population	
	Inotuzumab (N = 109)	**SoC (N = 109)**	**Inotuzumab (N = 164)**	**SoC (N = 162)**
Age, mean (SD)	NR	NR	45.9 (17.1)	46.0 (16.6)
Age, median (range)	47 (18.78)	47 (18–79)	46.5 (18–78)	47.5 (18–79)
Male, n (%)	61 (56)	73 (67)	91 (55.5)	102 (63.0)
Race[b], white, n (%)	76 (70)	79 (72)	112 (68.3)	120 (74.1)
ECOG PS, n (%)[c]				
• 0	43 (39)	45 (41)	62 (37.8)	61 (37.7)
• 1	50 (46)	53 (49)	81 (49.4)	80 (49.4)
• 2	15 (14)	10 (9)	21 (12.8)	20 (12.3)
• Missing data	1 (1)	1 (1)	0	1 (0.6)
Salvage-treatment phase, n (%)				
• First	73 (67)	69 (63)	111 (67.7)	104 (64.2)
• Second	35 (32)	39 (36)	51 (31.1)	57 (35.2)
• Missing data	1 (1)	1 (1)	2 (1.2)[d]	1 (0.6)[d]
Duration of first remission, n (%)				
• <12 months	62 (57)	71 (65)	98 (59.8)	108 (66.7)
• ≥12 months	47 (43)	38 (35)	66 (40.2)	54 (33.3)
Previous HSCT, n (%)	17 (16)	22 (20)	28 (17)	26 (18)
Number of previous induction therapies, n (%)				
• 1	75 (69)	69 (63)	112 (68.3)	104 (64.2)
• 2	33 (30)	39 (36)	50 (30.5)	57 (35.2)
• 3	1 (1)	1 (1)	2 (1.2)	1 (0.6)
Response to most recent previous induction therapy, n (%)				
• Complete response	78 (72)	74 (68)	121 (73.8)	111 (68.5)
• Partial response	9 (8)	7 (6)	11 (6.7)	10 (6.2)
• Treatment-resistant disease	17 (16)	18 (17)	28 (17.1)	30 (18.5)
• Progressive or stable disease	4 (4)	10 (9)	4 (2.4)	10 (6.2)

	ITT218 population[a]		**ITT population**	
	Inotuzumab (N = 109)	**SoC (N = 109)**	**Inotuzumab (N = 164)**	**SoC (N = 162)**
White cell count, per mm^3, median (range)	3,500 (0–47,400)	3,800 (100–51,000)	4,100 (0–47,400)	4,000 (100–68,800)
Peripheral blast count, per mm^3, median (range)[e]	175.4 (0–42,660)	39.3 (0–31,500)	107.6 (0–42,660)	30.0 (0–43,331.4)
• Missing data, n (%)	1 (1)	1 (1)	1 (0.6)	3 (1.9)
No circulating peripheral blasts, n (%)	42 (39)	48 (44)	71 (43.3)	74 (45.7)
Bone marrow blasts, n (%)				
• <50%	30 (28)	29 (27)	53 (32.3)	48 (29.6)
• ≥50%	77 (71)	78 (72)	109 (66.5)	113 (69.8)
• Missing data	2 (2)	2 (2)	2 (1.2)	1 (0.6)
CD22 expression, n (%)[f]				
• <90%	24 (22)	24 (22)	35 (21.3)	36 (22.2)
• ≥90%	74 (68)	63 (58)	107 (65.2)	93 (57.4)
• Missing data	11 (10)	22 (20)	22 (13.4)	33 (20.4)
Karyotype, n (%)[g]				
• Normal[h]	27 (25)	23 (21)	46 (28.0)	42 (25.9)
• Ph-positive	14 (13)	18 (17)	22 (13.4)	28 (17.3)
• T(4;11)-positive	3 (3)	6 (6)	6 (3.7)	7 (4.3)
• Other abnormalities	49 (45)	46 (42)	70 (42.7)	67 (38.9)
• Unknown or missing data	16 (15)	16 (15)	20 (12.2)	22 (13.6)

Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HSCT, haematopoietic stem cell transplantation; NR, not reported; Ph, Philadelphia chromosome; SoC, standard-of-care.
Notes: [a] The remission-analysis population includes the first 218 patients who underwent randomisation in the intent-to-treat population; [b] Data on race were provided by the trial centre; [c] ECOG PS scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing symptoms; [d] Includes salvage 3 up or missing; [e] The peripheral-blast count is the product of the number of peripheral blasts multiplied by 0.01 and the number of white cells multiplied by 1000; [f] CD22 expression was assessed at a central laboratory; [g] Karyotype was assessed at a local laboratory, although Philadelphia chromosome (Ph) positivity could be assessed at a central laboratory or local laboratory or through medical history; [h] The assessment of normal karyotype was based on a minimum of 20 metaphases.
Source: INO-VATE 1022 CSR[11]

The baseline characteristics between treatment groups were broadly similar, except that slightly more patients in the SoC arm were male and had a shorter duration of first remission (<12 months). The

median peripheral blast count was considerably lower in the SoC arm than the inotozumab arm (30.0 versus 107.6 mm^3). The average age of patients in the trial (47 years) was lower than the average age of R/R B-cell ALL patients generally seen in NHS practice. Age has a large influence on survival outcomes in R/R B-cell ALL, therefore, survival rates may not be as high in NHS practice as in the INO-VATE 1022 trial.

4.2.2 Summary of the quality of the included trials

Results of the quality assessment of the INO-VATE 1022 trial were tabulated on page 90 of the CS. This was a large open-label trial, with appropriate methods of randomisation and allocation concealment. Treatment groups were broadly similar at baseline. The analysis included an intention-to-treat analysis, which was appropriate, and there is no evidence to suggest that the authors measured more outcomes than they reported.

Remission outcomes were assessed by an independent Endpoint Adjudication Committee (EAC) for the initial ITT218 population, but not the full ITT population; CR/CRi was assessed by the trial investigators (who were not blinded to treatment group) for the full ITT population. However, results were broadly similar between the ITT218 population and full ITT population, therefore, the ERG does not consider this to have had any significant effect on the remission outcome results.

There was an imbalance in the number of drop-outs between treatment groups, with more patients randomised to the SoC group withdrawing from the trial prior to receiving study treatment. However, the company provided baseline characteristics of the [redacted] patients who dropped out of the trial prior to receiving study treatment, as well as a summary of efficacy results for the modified ITT (mITT) population (the ITT population excluding the [redacted] patients who dropped out), which were consistent with those for the full ITT population.

4.2.3 Summary of the results of the included trials

The two primary endpoints of the INO-VATE 1022 trial were remission outcomes (the proportion of patients who achieved CR/CRi) and overall survival. Secondary endpoints included duration of remission, progression free survival, rate of subsequent HSCT and the proportion of CR/CRi patients who also achieved minimal residual disease negativity. In addition, patient-reported outcomes and adverse events were reported.

Results were presented for the full ITT population (316 patients; 08/03/16 data cutoff) for all outcomes, and for the ITT218 population (the first 218 patients; 2/10/14 data cutoff) for remission outcomes. Adverse events were reported for the 'safety population' (also called the modified ITT

(mITT) population), which included all patients in the ITT population who received at least one dose of treatment; [redacted] patients randomised to the SoC group dropped out of the trial before receiving treatment, therefore, the safety population included 307 patients (164 in the inotuzumab arm and 143 in the SoC arm). The ERG consider the full ITT population results to be the most relevant, as they are more complete than the ITT218 population results, therefore, these results are reported below.

Remission outcomes

Statistically significantly more patients receiving inotuzumab achieved CR or CRi than patients receiving SoC [redacted] Table 3 presents the remission outcome results for the full ITT population, including the proportion of CR/CRi patients who achieved MRD negativity (presented in Tables 18 and 22 of the CS). The remission outcome results for the ITT218 population were presented in Table 17 of the CS and were broadly consistent with those for the full ITT population.

Table 3: Remission outcomes (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**	**Rate difference**	**p-value**
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	
CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	
CR/CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for rate; 97.5% CI for rate difference	[redacted]	[redacted]	[redacted]	
MRD negativity in CR/CRi patients	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; SoC, standard of care.
Source: INO-VATE 1022 CSR[11]

It should be noted that the remission outcomes were assessed by an independent Endpoint Adjudication Committee (EAC) for the initial ITT218 population, but not the full ITT population; CR/CRi was assessed by the trial investigators for the full ITT population. However, as results were broadly similar between the ITT218 population and full ITT population, the ERG does not consider this to have had any significant effect on the remission outcome results.

The CS emphasises the importance of MRD negativity as an outcome in R/R B-cell ALL. Of the patients who achieved CR/CRi, a statistically significantly greater proportion in the inotuzumab group

also achieved MRD negativity compared with the SoC arm, as shown in Table 3 above, and Table 22 of the CS. However, as discussed in Section 3.4, the clinical expert statement submitted by Professor Adele Fielding emphasised that "the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED", therefore, the results relating to MRD negativity should be interpreted with caution, particularly for patients receiving second salvage treatment, for whom MRD negativity has not been shown to be associated with better survival outcomes.[1]

Duration of remission and time to remission

For patients who achieved CR/CRi, the median duration of remission (DoR) was [redacted] months (95% CI: [redacted]) in the inotuzumab group and [redacted] months (95% CI: [redacted]) in the SoC group. The CS highlighted the fact that once patients proceeded to HSCT, no further bone marrow samples were collected, therefore, they were removed from the DoR analyses, reducing the reported DoR.

The median time from randomisation to achieving CR/CRi was [redacted] months (range [redacted] months) in the inotuzumab group and [redacted] months (range [redacted] months) in the SoC group. The DoR and time to remission results for the ITT218 population were broadly consistent with those for the full ITT population, reported in Tables 26 and 27 of the CS.

[redacted] the definition of DoR be extended to include all patients in the ITT population, with non-responders being given a duration of remission of zero. In this analysis, the median duration of remission was [redacted] in the inotuzumab group and [redacted] in the SoC group. These results were presented in Table 25 of the CS (for both the full ITT population and the ITT218 population) and a Kaplan-Meier plot for the duration of remission analysis [redacted] was presented in Figure 12 of the CS. The hazard ratio (HR) for duration of remission was statistically significantly in favour of the inotuzumab group, compared with the SoC group for the full ITT population [redacted]).

Subgroup analysis results

CR/CRi rate according to baseline patient characteristics

Pre-planned subgroup analyses were performed according to baseline patient characteristics, although subgroup analyses were only presented for the ITT218 population, rather than the full ITT population. Forrest plots were presented as Figures 14 and 15 in the CS. The ERG requested clarification on why some of the numbers in Figure 14 were inconsistent with those reported in Table 14 of the CS (patient baseline characteristics), the company stated that the data in Figure 14 were based on data using the Interactive Voice Response System (IVRS), whereas data in Table 14 were from case report forms.

The only patient characteristics that did not statistically significantly favour the inotuzumab arm were the subgroup of Ph+ patients and the subgroup of t(4;11)-positive patients. However, the numbers of patients in these analyses were small, which may account for the lack of statistical significance.

Overall survival

The median overall survival (OS) was 7.7 months (95% 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. Survival probabilities were presented in Table 19 of the CS and a Kaplan-Meier plot of overall survival was presented as Figure 8. 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 boundary of P=0.0208.

The CS stated that the OS data appeared to deviate from the proportional hazards assumption at around 15 months with the separation of curves in the Kaplan-Meier plots appearing after the median had been reached. Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. RMST is the mean survival time from randomisation to a clinically relevant time horizon (t*) equivalent to the area under the Kaplan-Meier curve up to the specified time. The time horizon used in the CS was the shorter of the maximum OS time in the two arms of the study, i.e. looking at the last censored event in each arm and taking the shortest, which was 24 months. In addition, a timepoint reflecting the maximum observation time from the treatment arms was also presented; 37.7 months. The ERG requested formal test evidence of non-proportionality in the overall survival data, as well as further justification for the choice of timepoint in the RMST analysis, along with analyses at earlier timepoints. In response, the company presented appropriate tests for non-proportional hazards, which were suggestive of non-proportionality, although based on only a few patients in the inotuzumab group surviving to later timepoints and the sudden drop off in the SoC group Kaplan-Meier curve at 15-20 months, based on a small number of deaths. However, the ERG accepts the company's argument for non-proportional hazards and the justification for using RMST

analyses, despite the exploratory, post-hoc nature of the analyses. The ERG is more concerned with the time horizon used in the RMST analyses. In response to the ERG's Points for Clarification, the company provided OS data based on the RMST analyses at additional timepoints, presented in Table 4. Summary of RMST for overall survival (ITT population)

Table 4: Summary of RMST for overall survival (ITT population)

[redacted]

Table 4 demonstrates that the RMST results are strongly dependent on the choice of truncation time, with little difference between the treatment groups in the 12 and 18 month analyses. [redacted].

The RMST analysis results presented in the CS were those for the truncation time of 37.7 months; median OS in the inotuzumab group was 13.9 months (standard error (SE): 1.1) and for SoC 9.9 months (SE: 0.9), with a difference of 3.9 months between groups (95% CI: 1.2 to 6.7), presented in Table 20 of the CS. However, the median OS presented for the SoC group was considerably higher than other estimates of OS, presented in Table 6 of the CS (range 3 to 5 months), suggesting that the RMST analysis appears to inflate OS.

Subgroup analysis results

MRD status

OS was considerably [redacted] in patients who achieved MRD negativity, than patients who did not; median OS was [redacted] months [redacted] for the [redacted] patients who achieved MRD negativity in the inotuzumab group and [redacted] months [redacted] for the [redacted] patients who achieved MRD negativity in the SoC group. It should be noted that these results were for all patients who achieved MRD negativity, not just those who received HSCT. Median OS was [redacted] months [redacted] for the [redacted] patients who did not achieve MRD negativity in the inotuzumab group and [redacted] months [redacted] for the [redacted] patients who did not achieve MRD negativity in the SoC group. These data are presented in Table 23 of the CS. The CS noted that the small number of MRD negative patients in the SoC group ([redacted] patients) means that these survival outcomes should be interpreted with caution. As discussed in Section 3.4, MRD negativity has not been shown to be associated with better survival outcomes in patients receiving second salvage treatment;[1] MRD negativity results were not provided separately for patients receiving first and second salvage treatment in the INO-VATE 1022 trial.

The CS also presents a Kaplan-Meier survival curve of OS by MRD status in CR/CRi patients treated with inotuzumab (Figure 10 of the CS); the difference in OS between MRD negative and MRD positive groups was not statistically significant.

Subsequent HSCT

Patients who received HSCT had longer OS than patients who did not. The CS stated that much fewer patients in the SoC arm received HSCT, therefore, SoC arm survival outcomes should be interpreted with caution. The CS stated that additional caution should be taken in interpretation as the patients who have undergone HSCT in the two trial arms are no longer a randomised comparison and that as the tails of the curves show separation, caution should also be made when comparing the medians. Overall survival following HSCT is presented in Figure 11 of the CS, [redacted] Further appraisal of the data on OS following HSCT is presented in the economic section of this report.

[redacted]

[redacted]

OS according to baseline patient characteristics

Pre-planned subgroup analyses were performed according to baseline patient characteristics for the full ITT population. A Forrest plot was presented as Figure 16 in the CS. The company stated that a comparison of the medians is not reflective of the whole survival distribution, due to the separation in the tails of the curves; therefore, these results should be interpreted with caution. There was no interpretation of Figure 16 presented in the CS.

The results [redacted]

Rate of subsequent HSCT

A statistically significantly higher proportion of patients in the inotuzumab group progressed to HSCT after study therapy, and prior to the start of any post induction therapy, than in the SoC group; [redacted] Details are presented in Table 5 (Table 24 in the CS).

Table 5: Subsequent HSCT in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
HSCT rate		
Patients with HSCT, n (%) [95% CI]	[redacted]	[redacted]
• Difference in HSCT rate between the two arms (95% CI) [p-value]	[redacted]	
Type of transplant, n (%)		
• Allogeneic	[redacted]	[redacted]
• Autologous	[redacted]	[redacted]
Type of conditioning therapy, n (%)		
• Myeloablative	[redacted]	[redacted]
• Reduced intensity	[redacted]	[redacted]

Key: CI, confidence interval; HSCT, haematopoietic stem cell transplantation; SoC, standard of care.
Source: INO-VATE 1022 CSR[11]

Additional results relating to HSCT and the proportion of HSCT patients who had achieved CR/CRi were provided by the company in their response to the ERG's Points for Clarification document. The additional results provided by the company were for all patients who received HSCT, whether or not they had received another intervening induction therapy before receiving HSCT (subsequent induction therapies received by patients were reported in Table 15 of the CS); therefore, a larger number of patients in both treatment groups, but particularly the SoC treatment group, had received HSCT in these results. These results are presented in Table 6.

Table 6: Subsequent HSCT in INO-VATE 1022 by CR/CRi status (ITT population)

Status	Inotuzumab (n=164)	Standard of Care (n=162)
HSCT		
Did not have HSCT	[redacted]	[redacted]
Achieved CR/CRi	[redacted]	[redacted]
Did not achieve CR/CRi	[redacted]	[redacted]
Had HSCT	[redacted]	[redacted]
HSCT and CR/CRi	[redacted]	[redacted]
HSCT but not CR/CRi	[redacted]	[redacted]

Source: INO-VATE 1022 CSR[11]

As shown in Table 6, [redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice, where patients have to have achieved CR/CRi to be eligible for HSCT. The ERG requested further information about the patients who received HSCT without having achieved CR/CRi. [redacted]

In addition [redacted] inotuzumab patients and [redacted] SoC patients who did not receive HSCT achieved CR/CRi; the ERG asked the company to provide reasons why a proportion of patients who achieved CR/CRi did not receive HSCT. The company responded that [redacted]

[redacted] Of the patients who achieved CR/CRi, [redacted] of the inotuzumab arm and [redacted] of the SoC arm received HSCT. The ERG's clinical advisor stated that the decision to perform HSCT is complex; this complexity reflects the need to use hard clinically meaningful endpoints, such as overall survival.

The figures used in the economic model were those reported for patients who received HSCT whether or not they had received another intervening induction therapy before receiving HSCT ([redacted] inotuzumab patients and [redacted] SoC patients in the safety population). The model grouped all HSCT patients together, regardless of CR/CRi status.

The company also provided the data presented in Table 6 for the ITT218 population, which were broadly similar to the results for the full ITT population.

Progression free survival

The CS stated that progression free survival (PFS) is considered to be a more appropriate indicator of a patient's duration of remission than the duration of remission analyses presented in the CS, because patients who proceeded to HSCT were removed from the analyses (because no further bone marrow samples were collected from them) and only patients who achieved CR/CRi were included in the pre-specified duration of remission analyses. However, proceeding to HSCT, without having achieved CR/CRi (which was more frequent in the SoC group than the inotuzumab group) was classed as a progression event in the INO-VATE 1022 trial (progression-free survival was defined as the time from date of randomisation to the earliest date of the following events: death, progressive disease, or starting a new induction therapy or post-therapy HSCT without achieving CR/CRi). The ERG does not consider proceeding to HSCT, without achieving CR/CRi, to be an appropriate progression event, as proceeding to HSCT is a positive outcome for patients. In addition, this definition means that the PFS results favour inotuzumab, as more patients in the SoC arm proceeded to HSCT, without having achieved CR/CRi.

The median PFS was 5.0 months (95% CI: 3.7 to 5.6) in the inotuzumab group and 1.8 months (95% CI: 1.5 to 2.2) in the SoC group. PFS outcomes were presented in Table 21 of the CS and a Kaplan-Meier plot of PFS was presented as Figure 9. The progression event that occurred most frequently in the SoC arm was [redacted]. The progression event that occurred most frequently in the inotuzumab arm was [redacted]

Patient report outcomes

Patient-reported outcomes were assessed 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), which were appropriate tools. Completion rates were adequate (the proportion of patients in the trial who completed the questionnaires), although the number of patients who remained on treatment decreased considerably after the first cycle of treatment, therefore the number of patients completing the questionnaires reduced; the actual numbers of patients completing the questionnaires was not reported. In addition, it should be noted that for patients who discontinued treatment, particularly those who discontinued due to adverse events or disease progression, the patient-reported outcome scores are likely to have been lower than for those who continued treatment and continued completing the questionnaires. The open label design of the trial inevitably introduces potential bias for subjective outcomes such as quality of life.

The baseline patient-reported outcome scores were comparable between treatment groups for most dimensions, presented in Table 28 of the CS. Patient-reported outcome results were presented as the estimated mean change from baseline, rather than the actual scores after treatment for both treatment groups, therefore, the actual change from baseline and differences in scores between groups could not be assessed. The data presented indicated a greater 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 (although the difference was only statistically and/or clinically significant for a few dimensions). [redacted] However, the limitations in reporting, in terms of the number of patients who completed questionnaires after treatment and the lack of reporting of actual quality of life scores after treatment, mean that these results should be interpreted with caution.

Discontinuation rates

In the ITT population 76.2% patients in the inotuzumab group and 90.7% patients in the SoC group permanently discontinued from the study, the most common reason for discontinuation was patient death (74.4% inotuzumab patients and 79.6% SoC patients). A total of 54 patients were still being followed-up at the database cut-off date of 8 March 2016; 39 in the inotuzumab group and 15 in the SoC group.

A total of [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group discontinued treatment due to adverse events. [redacted]

[redacted]

A further [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group had treatment delays due to adverse events. [redacted]

[redacted]

Adverse events

Adverse event data were presented for all treatment cycles and for Cycle 1 only; the average number of cycles of treatment in the inotuzumab group was 3, compared with an average of 1 cycle in the SoC group. Adverse event data for subsequent treatments received by patients were not collected (subsequent induction therapies received by patients were reported in Table 15 of the CS).

Across all cycles, [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs). During Cycle 1 [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs).

TEAEs by system organ class that occurred in ≥5% patients in either treatment arm were presented in Table 33 of the CS. Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm than the SoC arm [redacted]. The CS states that VOD rates were particularly high in Japanese centres, with [redacted] inotuzumab patients and [redacted] SoC patients experiencing VOD after HSCT, and describes the differences between Japanese practices and UK practice, stating that VOD rates in the UK would be expected to be lower. However, of the [redacted] inotuzumab patients who experienced VOD, [redacted], therefore, VOD cannot be dismissed due to different practices between Japanese centres and the UK. The CS also states that the rate of VOD was higher in patients who had received a prior HSCT, therefore, rates of

VOD would be expected to be lower in clinical practice, as second HSCT is not currently funded under NHS England. However, the new NHS England report 'Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages)' means that patients who have already received prior HSCT may now be eligible for second HSCT for relapsed disease. [redacted] Treatment of VOD is associated with very high costs.

Across all cycles, Grade ≥3 TEAEs were reported by [redacted] patients in the inotuzumab group and [redacted] patients in the SOC group. During Cycle 1 [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported Grade 3 or 4 TEAEs. A summary of Grade ≥3 TEAEs that occurred in ≥2% patients in either treatment arm were presented in Table 35 of the CS. Most Grade ≥3 TEAEs were more frequent in the SoC arm than the inotuzumab arm, again with the exception of VOD; [redacted]

4.2.4 Supporting data from non-RCTs

Supporting evidence from two non-RCT studies was presented; study NCT01363297 was a single-arm US study which comprised a dose finding study and a dose-expansion study[6] and the MDACC study was a US observational study of patients with R/R B-cell ALL, from which data for 90 patients treated with inotuzumab were presented in the CS.[5] Both of these studies included a proportion of patients who received inotuzumab as Salvage 3 or later therapy (38% of patients in the NCT01363297 study and 30% of patients in the MDACC study); therefore, patients in these studies had a poorer prognosis than those in the INO-VATE 1022 trial.

The number of patients included in the initial dose finding phase of the NCT01363297 study was very small (24 patients) and inotuzumab was only administered at the recommended dose of 1.8 mg/m^2 per cycle in 9 patients, 8 of which achieved CR/CRi (88.9%) and 4 proceeded to HSCT. In Phase II of

this study, 35 patients received inotuzumab at a dose of 1.8 mg/m^2 per cycle, of which 24 (68.6%) achieved CR/CRi and 8 proceeded to HSCT.

The MDACC observational study included 90 patients who received inotuzumab, although the first 49 patients were treated with a single-dose (1.3-1.8 mg/m^2), rather than the recommended weekly schedule (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15). This study also included some patients aged less than 18 years. In an analysis of the MDACC data including only the 75 adult patients, 41 (54.7%) achieved CR/CRi or CRp (defined as CR without platelet recovery to $\geq 100 \times 10^9$/L).

4.3 Conclusions of the clinical effectiveness section

The CS evaluation of inotuzumab was primarily based on one reasonably good quality RCT; the INO-VATE 1022 trial, which compared inotuzumab to SoC, which was the investigator's choice of FLAG, CM or HIDAC. However, the trial only included patients who were suitable for intensive therapy and were due to receive either Salvage 1 or Salvage 2 therapy, which is only a subset of the anticipated licenced population. No comparative evidence has been presented for the use of inotuzumab in patients who require third or later salvage treatment, or who are not fit for intensive treatment or may be treated with palliative intent. In addition, two of the comparator treatments in the trial (CM and HIDAC) are not used in current NHS practice, whereas two treatments that are used in NHS practice, and were specified in the NICE scope, were not used as comparators within the trial (clofarabine-based combination chemotherapy for Ph- patients and TKIs alone or in combination with clofarabine-based chemotherapy for Ph+ patients). The NICE scope also included a "best supportive care (including palliative care)" comparator, for people who are unable to tolerate chemotherapy. However, as stated previously, patients who were unfit for intensive therapy were not included in the INO-VATE 1022 trial.

The trial demonstrated that inotuzumab is effective at improving remission outcomes, with significantly more patients achieving CR/CRi than patients receiving SoC ([redacted] versus [redacted]). Inotuzumab was also associated with a statistically significantly higher proportion of patients progressing to HSCT after study therapy than SoC ([redacted]. However, [redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice, where patients have to have achieved CR/CRi to be eligible for HSCT. The economic model grouped all HSCT patients together, regardless of CR/CRi status. In addition [redacted] inotuzumab patients and [redacted] SoC patients did not receive HSCT, despite achieving CR/CRi; the ERG's clinical advisor stated that the decision to perform HSCT is

complex; this complexity reflects the need to use hard clinically meaningful endpoints, such as overall survival.

The OS data were less convincing; median OS was 7.7 months (95% 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 CS stated that the OS data appeared to deviate from the proportional hazards assumption at around 15 months with the separation of curves in the Kaplan-Meier plots appearing after the median had been reached. Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. RMST results were strongly dependent on the choice of truncation time, [redacted] The RMST analysis results presented in the CS were those for the truncation time of 37.7 months; median OS in the inotuzumab group was 13.9 months (standard error (SE): 1.1) and for SoC 9.9 months (SE: 0.9), with a difference of 3.9 months between groups (95% CI: 1.2 to 6.7). The median OS presented for the SoC group was considerably higher than other estimates of OS, presented in Table 6 of the CS (range 3 to 5 months), suggesting that the RMST analysis appears to inflate OS.

Data presented on patient-reported outcomes indicated a greater 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 (although the difference was only statistically and/or clinically significant for a few dimensions). [redacted] However, limitations in reporting patient-reported outcomes, in terms of the number of patients who completed questionnaires after treatment and the lack of reporting of actual quality of life scores, mean that these results should be interpreted with caution.

Across all cycles, [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs). Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm than the SoC arm [redacted]. [redacted] Across all cycles, Grade ≥3 TEAEs were reported by [redacted] patients in the inotuzumab group and [redacted] patients in the SOC group.

Most Grade ≥3 TEAEs were more frequent in the SoC arm than the inotuzumab arm, again with the exception of VOD; [redacted]

[redacted]

A total of [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group discontinued treatment due to adverse events. A further [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group had temporary discontinuations due to adverse events.

The CS presented supporting evidence from two non-RCT studies; study NCT01363297 and the MDACC study. The results were not as favourable in these studies as in the INO-VATE 1022 trial. However, both studies included patients who received inotuzumab as Salvage 3 or later therapy, therefore, patients in these studies had a poorer prognosis than those in the INO-VATE 1022 trial. The supporting evidence was much less robust than the INO-VATE 1022 trial, both studies were small, did not include a non-inotuzumab control group and a proportion of patients did not receive inotuzumab at the recommended dosing schedule.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation[12] and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios requested from the company or independently undertaken by the ERG to further explore these uncertainties.

The company's economic submission included:

- A description of each systematic review conducted to identify published evidence on the cost-effectiveness, HRQoL/utilities and resource usage/costs (CS, Sections 5.1, 5.4, 5.5) with further details presented in separate appendices (CS, Appendices 3, 8, 9).
- A report on the de novo economic evaluation conducted by the company. The report included a description of the patient population and the model structure (CS, Section 5.2); the clinical parameters used in the economic model (CS, Section 5.3); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section 5.4); the cost and healthcare resource use identification, measurement, and valuation (CS, Section 5.5); a summary of the inputs and assumptions used in the model (CS, Section 5.6); the cost-effectiveness results for the base-case (CS, Section 5.7) and sensitivity analyses (CS, Section 5.8); an overview of any subgroup analyses (CS, Section 5.9); the methods of validation (CS, Section 5.10); and the final interpretation and conclusion of the economic evidence (CS, Section 5.11).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, alongside additional data and analyses requested by the ERG.
- An updated Excel-based model correcting minor errors and incorporating the additional scenario analyses requested by the ERG.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the National Health Service Economic Evaluations Database [NHS EED] and the Health Technology Assessment Database [HTAD]) were searched between 5 and 6 September 2016. The search strategies used for each database were reported in Appendix 3 of the CS.

In addition, bibliographies of key systematic reviews, economic models and HTAs were screened and the proceedings of four conferences from 2014 to 2016 were hand searched; British Society for Haematology (BSH), European Haematology Association (EHA), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress and the ISPOR Annual International Congress. The following websites were also searched: European Medicines Agency (EMA), US Food and Drugs Administration (FDA), NICE, Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG).

The structure of the search strategies for MEDLINE, EMBASE and the Cochrane Library were appropriate. Disease terms for RR B-cell ALL were combined with terms for inotuzumab or other relevant drugs used to treat RR B-cell ALL from the NICE scope (blinatumomab, clofarabine, dasatinib, imatinib, ponatinib, FLAG, FLAG-HAD, HIDAC). The searches of MEDLINE In Process and EconLit were also appropriately structured. The MEDLINE In Process search contained disease terms only, limited to those studies not already in MEDLINE. The search of EconLit contained search terms for the disease only.

The database searches were limited to studies published since 2000. A study design search filter designed by SIGN was used to limit retrieval to economic studies in MEDLINE and EMBASE and an English language limit was also applied.

The strategies contained relevant subject headings, text word searches and synonyms and all search lines were combined correctly. A possible typing error was identified in the search strategies: lympholeuci* would have been more appropriately truncated as lympholeuc*. In the search of MEDLINE In Process a lack of truncation was noted which would have affected the sensitivity of this search, however truncation was used appropriately in the other databases searched.

The methods used to search for studies via conference proceedings and websites were not provided by the company in the submission nor in their response to ERG's points for clarification. Therefore, although the conference proceedings sources and websites searched were appropriate, it is not possible to assess the methods used to search these sources.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria are reported in sections 5.1.2., 5.4.3.2 and 5.5.1.2 of the CS and followed the usual PICOS framework (CS, Tables 37, 54 and 59). Studies that assessed mixed disease populations containing separate R/R ALL data and those that had at least one relevant treatment arm were included in the review. Articles were independently assessed by one reviewer against each eligibility criteria. Any uncertainty regarding the inclusion of studies was checked and judged by a second independent reviewer.

5.1.3 Studies included and excluded in the cost-effectiveness review

A total of 602 potentially relevant articles were identified in the cost-effectiveness review. 587 of these were subsequently excluded at the primary screening stage. The remaining 15 studies were assessed in full. Only one of these articles was included in the final review. An additional 9 articles were identified and included from the grey-literature searches.

Of the 10 total publications included in the cost-effectiveness review, two were abstracts and 8 were HTA appraisals of ponatinib (n=3), blinatumomab (n=3) and dasatinib (n=2). No previously published studies of the cost-effectiveness of inotuzumab were identified.

5.1.4 Conclusions of the cost effectiveness review

The company's search did not identify any relevant economic assessments of inotuzumab for the treatment of R/R B-cell ALL. Therefore, the ERG considers the *de-novo* cost-effectiveness analysis reported in the CS to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary of company's submitted economic evaluation

An overview of the company's economic evaluation is presented in Table 7. The results of the checklist used to assess the quality of the submission are reported in Appendix 10.1.

Table 7: Overview of company economic evaluation

	Approach	Source / Justification	Location in CS
Model	Decision model based on a partitioned survival approach. Separate health states are used based on CR/CRi and HSCT outcomes. 60 year (lifetime) time horizon with 28-day cycles.	The structure based on remission and HSCT outcomes reflects the treatment goal of induction therapies to successfully bridge to a potentially curative treatment option such as HSCT.	Section 5.2.2; p159-166
States and events	The model consists of four main mutually exclusive health states: (i) No CR/CRi & no HSCT, (ii) CR/CRi & no HSCT, (iii) HSCT & Post-HSCT and (iv) death. Additional tunnel states are used within the HSCT & Post-HSCT state to reflect the waiting period for HSCT. Separate sub states are also used within each main health state (excluding death) to represent progression-free and progressed disease.	Remission and HSCT were considered the main treatment goals and these intermediate outcomes were considered to determine longer term quality of life, survival and costs. The modelling approach was reported to be validated by clinical advisors.	Section 5.2.2; p159-166
Comparators	The standard of care (SoC) was based on the investigators choice arm from the INO-VATE 1022 trial. The company assumed that the FLAG regimen used in the NHS would include idarubicin (FLAG-IDA) and that Ph+ patients would also receive a TKI (imatinib) in addition to conventional chemotherapy.	The inclusion of the regimens within the SoC was considered by the company to be consistent with the final scope from NICE. Clinical advice to the company considered that the clinical outcomes observed in INO-VATE 1022, along with the majority of patients receiving FLAG, were representative of the current standard of care within the UK. The company excluded BSC as a comparator on the basis that "inotuzumab is suitable as a bridge to potentially curative therapy (usually HSCT), patients who are unfit for intensive therapy, such as chemotherapy-based treatments, will also be unfit for transplantation".	Section 5.2.3; p166-169
Natural History	CR/CRi and HSCT outcomes (and waiting times) were derived from the investigator's choice arm (safety dataset) from INO-VATE 1022. Parametric survival modelling using covariates was used to	Remission and HSCT were considered the main treatment goals and were assumed to determine longer term quality of life and survival estimates. The inclusion of covariates in the parametric survival models	Section 5.2.2; p159-166 Section 5.3; p169-197

	estimate survival functions for PFS and OS for each separate health-state according to CR/CRi and HSCT outcomes. After a specified time period (3-years in the base-case) patients in the HSCT & Post-HSCT state were assumed to be 'cured' and general population mortality risks from lifetables subsequently applied.	enabled additional exploratory analysis evaluating the impact of different prognostic factors. Separate justification was provided for each included covariate and validated by clinical advisors to the company. The best-fitting parametric curves were identified through visual inspection, statistical goodness of fit and assessment of clinical plausibility. The modelling approach and associated 'cure' assumptions were reported to be validated by clinical advisors	
Treatment effectiveness	Remission and HSCT outcomes (and waiting times) were derived from the inotuzumab arm (safety dataset) from INO-VATE 1022. Approach to modelling PFS and OS as described in natural history.	The INO-VATE 1022 trial demonstrates that inotuzumab is associated with significantly higher rates of CR/CRi, allowing significantly more patients to progress to potential curative therapy. Approximately 95% of the QALY gains with inotuzumab are derived from the 'HSCT and post HSCT' state. These differences were justified based on data from INO-VATE 1022 demonstrating (inotuzumab vs SoC): (i) a higher rate of HSCT; (ii) improved survival post-HSCT. The company acknowledged the limited data available concerning the assumption of improved survival post-HSCT and explored an additional scenario where this was assumed to be independent of treatment and dependent on MRD outcomes.	Section 5.2.2; p159-166 Section 5.3; p169-197
Adverse events	Inclusion criteria for adverse events in the model were any Grade ≥3 event experienced by ≥5% of patients in either treatment arm of INO-VATE 1022. VOD rates in the base-case were derived from INO-VATE 1022 excluding Japanese patients.	Adverse event rates were based on the recorded events in INO-VATE 1022. The exclusion of Japanese patients for VOD was justified based on differences in practice concerning conditioning regimens and to increase generalisability to the NHS.	Section 5.4.4; p209-211
Mortality	Parametric curves were used to extrapolate PFS and OS data within the 'No CR/CRi & no HSCT' and 'CR/CRi & no	A cure point of 3 years was considered most appropriate based on clinical judgement and visual assessment of the	Section 5.3.1; p170-173 Section 5.3.2; p174-178 Section 5.3.3; p179-184 Section 5.3.4; p184-187

	HSCT' states. For the 'HSCT & Post HSCT state', parametric survival curves were used to extrapolate survival up to a chosen 'cure' point. Cure points ranging from 2 to 5 years were considered and their validity discussed with a clinical expert. General population all-cause mortality rates for England and Wales (ONS 2016) were applied after the cure point to the 'HSCT & Post HSCT' state.	parametric survival functions. All-cause mortality rates were obtained from the UK life tables (ONS 2015).	Section 5.3.4; p188-191 Section 5.3.5; p192-197
Health-related quality of life	Health-state utilities were assigned to each health state and the separate sub states (progression-free and progressed).	EQ-5D data from the INO-VATE 1022 trial were used to inform HRQoL estimates for the progression-free period in the 'No CR/CRi & no HSCT' and 'CR/CRI & no HSCT' states. External literature was used to estimate utility of patients who received HSCT and was assumed to be treatment independent but varied according to time following HSCT. HRQoL decrements due to adverse events (excluding VOD) were assumed to be captured in the EQ-5D data from INO-VATE 1022. Decrements for VOD were obtained from the literature. Utilities assigned to the progression sub-state were derived from external literature.	Section 5.4.5; 211-214
Resource utilisation and costs	Resource use and costs included: drug acquisition and administration; management of adverse events; HSCT costs (initial procedure and follow-up); subsequent treatment costs and terminal care costs.	Resource use and costs associated with drug acquisition was based on the dosing in the INO-VATE 1022 trial (assuming no vial sharing). Additional scenarios were presented for inotuzumab based on a maximum of three cycles to reflect anticipated use in clinical practice. Additional costs were included for idarubicin (FLAG-IDA) and TKIs (Ph+ patients only) with dosing based on their SPCs. Drug administration costs for the SoC regimens were based on length of stay assumptions informed by the administration periods specified in the respective	Section 5.5; p215-238

		SPCs. Inotuzumab was assumed to be administered in an outpatient setting. Costs associated with HSCT (initial procedure and follow-up) were derived from the literature. Costs for adverse events were applied to all patients as a lump sum in Cycle 0, adverse event costs post-HSCT were applied to patients in the first cycle after their HSCT. Subsequent induction treatments were derived directly from data from INO-VATE 1022 (ITT dataset). End of life costs were based on costs from PSSRU (2016) reported in the final year of life and were assumed to incorporate the cost of treating a progressed patient. Unit costs were based on the literature, NHS Reference costs, the monthly index of medical specialties (MIMS) and the Department of Health's electronic market information tool (eMit). Where appropriate, unit costs were inflated to 2015/2016 prices.	
Discount rates	1.5% for utilities and costs (base case). Conventional 3.5% discount rates were presented as a scenario.	NICE Methods Guide	Section 5.2; p165-166
Population and Subgroups	No formal subgroups were presented. Instead, covariate analysis was used to inform exploratory assessments according to specific patient characteristics.	The final scope did not specify specific populations and subgroups. The impact of covariates is presented as part of exploratory analyses.	Section 5.9; p257
Sensitivity analysis	Deterministic sensitivity analysis was performed on a series of model parameters. Probabilistic sensitivity analysis and scenario analyses were also performed.	NICE reference case	Section 5.8; p248-257

Key: AUC: Area under the curve; HSCT: Haematopoietic stem cell transplant; CR: Complete response; CRi: Complete response with incomplete count recovery; PFS: Progression free survival; OS: Overall survival; HRQoL: Health-related quality of life; FLAG: Fludarabine, cytarabine, and granulocyte colony-stimulating factor; CM: Cytarabine & mitoxantrone; HIDAC: High dose cytarabine; ONS: Office for national statistics; ALL: Acute lymphoblastic leukaemia; EQ-5D: EuroQol 5 dimension questionnaire; VOD: Veno-occlusive liver disease; SMC: Scottish medical consortium; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

5.2.1 The company's economic evaluation compared with the NICE reference case checklist

Table 8 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 8: NICE reference case

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	The NICE scope defined comparators as follows: Philadelphia-chromosome-negative ALL: • FLAG-based combination chemotherapy • clofarabine-based combination chemotherapy (not appraised by NICE but funded via the CDF) Philadelphia-chromosome-positive ALL: • Tyrosine kinase inhibitors (TKIs) alone or in combination with FLAG or clofarabine-based chemotherapy For people who are unable to take chemotherapy: • Best supportive care (including palliative care)	Partially	The comparators in the model included: Philadelphia chromosome-negative ALL: • FLAG-based combination chemotherapy Philadelphia chromosome-positive (Ph+) ALL • A TKI in combination with FLAG-based chemotherapy The comparator was labelled as chemotherapy-based "*standard of care*" and informed by the comparator arm (investigator's choice) in the INO-VATE phase III trial: FLAG: n=[redacted] ([redacted]%) CM: n=[redacted] ([redacted]%) HIDAC: n=[redacted] ([redacted]%) Omitted comparators from the NICE scope included: • Clofarabine • TKIs alone • Best supportive care The ERG considers that clofarabine and TKIs used alone are potentially relevant comparators used within standard NHS practice. The ERG notes that the exclusion of BSC is consistent with the company's view that inotuzumab will be used as a bridging therapy and hence patients would have to be sufficiently fit for conventional chemotherapy and potentially HSCT. However, this appears a restricted population compared to the anticipated license.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective - costs	NHS and PSS	Yes	
Perspective - benefits	All health effects on individuals	Yes	
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	The economic model had a life-time horizon of 60 years. No patients were expected to be alive beyond this period. The long-term time horizon relies on a 'cure' based assumption.
Synthesis of evidence on outcomes	Systematic review	Yes	
Outcome measure	QALYs	Yes	

Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Utilities for the states defined by no subsequent HSCT ('No CR/CRI & no HSCT' and 'CR/CRi & no HSCT') were derived from the EQ-5D data captured directly from within the INO-VATE 1022 trial. Health state utilities for post-progression, post-HSCT and an adverse event (VOD) were obtained from the literature and past appraisals.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	
Source of preference data	Representative sample of the public	Yes	
Discount rate	3.5% on costs and health benefits	No	Costs and benefits have been discounted at 1.5% per annum in the base case analysis. However, the reference case 3.5% discount rate is explored in scenario analyses.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was conducted as well as deterministic sensitivity analyses. Mean increment results for the probabilistic sensitivity analysis were presented as well as graphical results using scatter plots, cost-effectiveness acceptability curves and tornado diagrams.
NHS - National Health Service; PSS - personal social services; QALY - quality-adjusted life years; HRQoL - health-related quality of life; NICE - National Institute for Health and Care Excellence; FLAG - Fludarabine, Cytarabine, and Granulocyte Colony-Stimulating Factor; CM - Cytarabine & Mitoxantrone; HIDAC; High dose cytarabine; TTO: Time Trade Off			

5.2.2 Population

The INO-VATE 1022 trial population was the primary source of data used to inform the cost-effectiveness model. As previously stated in Section 3.1, the population considered in the INO-VATE 1022 trial appears more restrictive than that specified within the NICE scope and also the anticipated licenced population for inotuzumab defined in the draft SPC. Consequently, the cost-effectiveness analysis is restricted to a subset of adults with R/R B-cell ALL; those who are sufficiently fit for intensive therapy, such as chemotherapy-based treatments and transplantation.

Although no subgroup populations were specified in the final scope issued by NICE, a series of patient subgroups were considered within a set of exploratory analyses.

5.2.3 Interventions and comparators

The dosing of inotuzumab implemented within the model was in accordance with the administration schedule used in INO-VATE 1022. A separate scenario analysis was also presented based on a maximum 3 cycles which the company expected to be recommended in the final SPC. As discussed in

Section 3.2, the ERG considers the schedule used within the INO-VATE 1022 study to be consistent with the draft marketing authorisation and importantly ensures consistency in the source of efficacy data (INO-VATE 1022) and costing assumptions applied within the model.

The comparators were based on the investigator's choice arm used in the INO-VATE 1022 trial, comprising one of the following three regimens: FLAG, CM or HIDAC. Hence, approximately [redacted] of patients were assumed to receive FLAG and [redacted] and [redacted] of patients were assumed to receive CM and HIDAC, respectively.

The company justified using the investigator's choice arm to represent the current standard of care (SoC) on the basis that while clinician feedback and literature suggest that FLAG-based combination chemotherapy regimens are established clinical practice for the majority of adults with R/R B-ALL, treatment decisions are also tailored to the individual patient. The company also considered that INO-VATE 1022 provided the most robust source to compare inotuzumab and FLAG-based regimens. As noted in Section 3.3, neither CM nor HIDAC were included in the NICE scope and the clinical advisor to the ERG did not consider that either treatment regimen reflects current NHS practice.

Within the economic model, the company included the addition of idarubicin to the FLAG regimen, since FLAG-IDA is widely administered in a UK setting. The ERG's clinical advisor confirmed that the use of FLAG-IDA would predominate in the UK. The company further assumed that the efficacy observed for FLAG in the INO-VATE 1022 trial would be equivalent to the efficacy for FLAG-IDA. This was justified on the basis of a small study (n=105) which showed no significant difference in outcomes between FLAG and FLAG-IDA.[13]

In line with final NICE scope, the company also included TKIs (in combination with the SoC chemotherapy) as a comparator in the model for Ph+ patients. However, the company stated that there is limited efficacy data concerning the effectiveness of TKIs after further lines of therapy. Consequently, while the company included the additional costs of TKI for Ph+ patients, no adjustment was applied to the efficacy estimates derived from INO-VATE 1022. The ERG considers that this approach is potentially optimistic in relation to the subsequent cost-effectiveness estimates for inotuzumab. In the absence of appropriate efficacy data from the INO-VATE 1022 trial to reflect the inclusion of TKIs assumed in the model, the ERG considers that it is more appropriate to keep the cost assumptions consistent with the efficacy data in the model.

As stated in Sections 2.2 and 3.3, clinical advice received by the ERG was that clofarabine is used in UK clinical practice and is efficacious, therefore, should have potentially been a comparator in the submission.

5.2.4 Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS). The time horizon used in the model was 60 years, which is assumed to represent a lifetime horizon. This was justified by the company based on the curative potential of HSCT and the need to fully capture lifetime costs and consequences. The ERG considers the use of a lifetime horizon to be appropriate but considers that there exist significant uncertainties relating to the extrapolation assumptions and the 'cure' assumption employed within the economic model. The ERG does not consider that these uncertainties have been fully addressed in the company submission.

A discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base case. The NICE Methods Guide states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years). The company justified the use of a 1.5% discount in their base-case based on the assumptions that HSCT can potentially restore patients to normal life expectancy. Results were also presented using the conventional reference case discount rate of 3.5% as a separate scenario within the company submission. The ERG considers that the company base case assumptions regarding progression and quality of life post HSCT are not consistent with the criteria for applying a discount rate of 1.5% (Section 5.2.7), and that receipt of HSCT does not restore patients to normal life expectancy in near full health (Section 5.2.6.1 and 5.2.7).

5.2.5 Model structure

In the absence of previously published cost-effectiveness analyses of inotuzumab, the company undertook a *de-novo* economic evaluation. The submission is based on a decision model with a Markov health state structure but with state membership determined using a partitioned survival modelling approach. Partitioned survival models are conceptually similar to state transition (Markov) models in that they are characterised by a series of health states with associated state values. However, they differ in the way that the proportion of patients in each health state at each time point (state membership) is determined. In state transition models, state membership is usually determined using matrices of transition probabilities which describe the probability an individual will make each

transition in a given time period. In the partitioned survival approach, state membership is obtained directly from a set of non-mutually exclusive survival curves.

Figure 2 reports the model structure used by the company. The model comprises four main mutually exclusive health states:

(i) *No CR/CRi & no HSCT*;

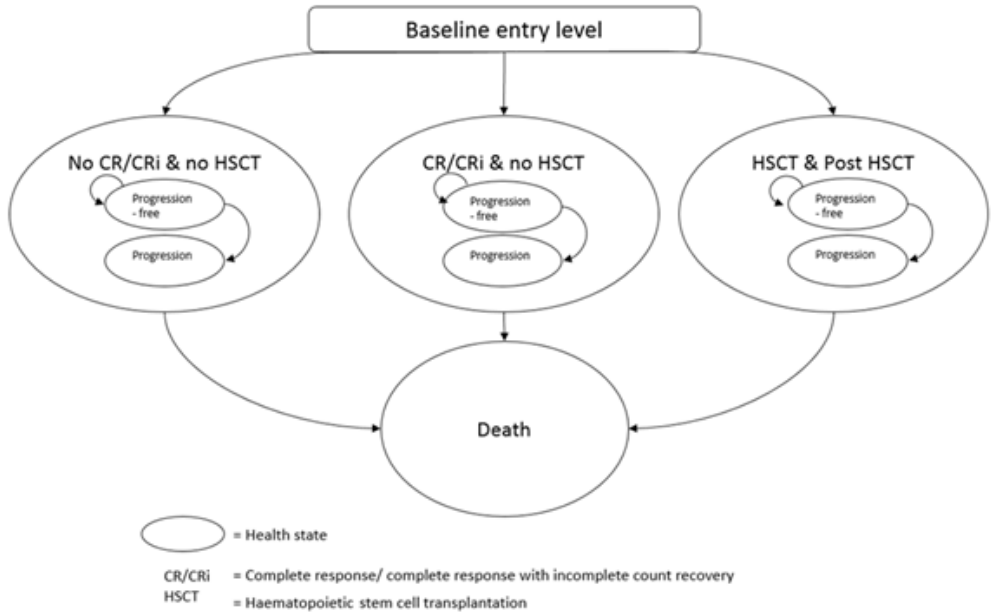
(ii) *CR/CRi & no HSCT*;

(iii) *HSCT & Post-HSCT* (which included all patients who received HSCT whether they were CR/CRi or No CR/CRi) and;

(iv) *death*.

Within each of these main health states (excluding 'death'), progression-free and progressed disease were incorporated as separate sub-states. The model uses a cycle length of 28 days with a half-cycle correction applied.

Figure 2: Schematic of company model structure



CS, Figure 23 - p160

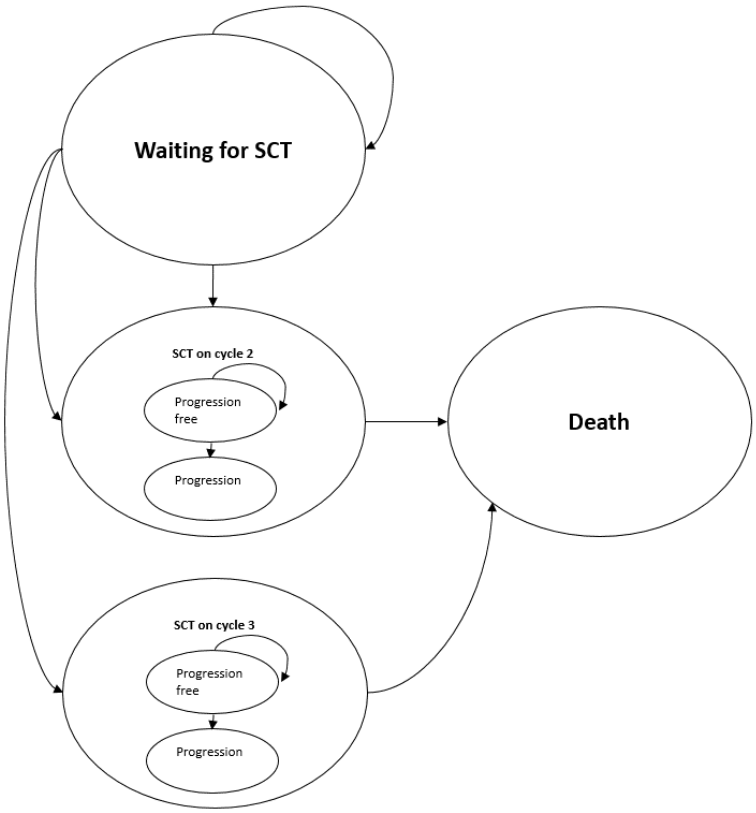
Patients enter the model in Cycle 0 (baseline entry level) which represents the point at which treatment with inotuzumab or SoC begins. During the first cycle of the model (28 days) patients are assumed to transition to one of the three main health states based on remission (CR/CRi) and

subsequent HSCT status: (i) *No CR/CRi & no HSCT*; (ii) *CR/CRi & no HSCT*; (iii) *HSCT & Post-HSCT*. The company acknowledged that assuming response status was determined within the initial cycle was a simplification. However, the company considered this assumption was broadly in line with the INO-VATE 1022 trial where the majority of patients who achieved CR/CRi did so during the period of the 1st cycle and [redacted] had by the 3rd cycle.

Although the company employed a simplifying assumption regarding the timing of transitions to these three health states, additional tunnel states were incorporated within the *HSCT & Post-HSCT* state to more accurately capture the subsequent timing of HSCT. The tunnel states were used to characterise the variability in the timing of the HSCT procedure in the INO-VATE 1022 study; up to [redacted] model cycles ([redacted] months) for inotuzumab and [redacted] model cycles ([redacted] months) for SoC.

A schematic of the tunnel states (across 2 cycles) incorporated within the *HSCT & Post-HSCT* state is reported in Figure 3. At the start of Cycle 1, all patients in the *HSCT & Post-HSCT* state enter the *Waiting for SCT* state. In subsequent cycles, patients can either remain in *Waiting for SCT* state or move to the *SCT* state. Patients in the *Waiting for SCT* state are assumed to be progression free. A total of [redacted] separate tunnel states are used to ensure that the proportion of patients receiving HSCT at each subsequent cycle in the model precisely matched the data from the INO-VATE 1022 trial.

Figure 3: Schematic of the tunnel states used in the HSCT and post HSCT state



CS, Figure 24 – p163

Key: SCT, stem cell transplant

Following the transition to one of the 3 main health states, subsequent transitions within the separate sub-states (progression-free, progression) and to the separate '*death*' state were informed by a series of separate parametric survival curves for PFS and OS (Section 5.2.6). The PFS survival curve is used directly to estimate the proportion of patients remaining in the progression-free sub-state over time. State membership for the death state is simply 1 minus the OS curve at each time point. For the progression sub-state, state membership is derived as the difference between the OS and the PFS curve at each time point, as this provides the proportion of patients who are alive but not progression-free.

Although the company describes their model as an 'area-under-the-curve, partitioned survival model', the modelling approach might be better described as a hybrid model since it combines elements of a decision-tree model and a partitioned survival modelling approach. That is, a simple decision-tree is used to determine the initial allocation of patients into one of the 3 main health states. Following this allocation, subsequent transitions from each of these health states are determined by a series of

separate survival functions specific to each state. Hence, the model structure and associated parametric survival modelling separates the patient population in INO-VATE 1022 trial into three separate sub-populations. The sub-populations and their respective sizes in the safety (modified ITT) data set are:

1. No CR/CRi & no HSCT ([redacted])
2. CR/CRi & no HSCT ([redacted])
3. HSCT & Post HSCT ([redacted])

The company stated that the model structure reflects the disease area where the main treatment goal in R/R B-cell ALL is to bridge patients to a potentially curative treatment such as HSCT and that remission is normally a pre-requisite for this. Since HSCT provides the best chance of long term survival, the company asserts that achieving CR/CRi is a key outcome and concludes that: "*the high CR/CRi rates seen within the INO-VATE 1022 trial illustrate inotuzumab's benefit patients in acting as a bridge to potentially curative therapy, so a key objective of the model was to accurately reflect this treatment benefit*" (CS, p159). Although the submission states that the model has been validated by multiple UK clinical experts as applicable to the decision problem, no details are provided in the main submission concerning the model conceptualisation process and the role of experts in validating the final model structure.

An important structural issue identified by the ERG is the absence of any explicit structural link in the proposed model between remission outcomes (CR/CRi) and HSCT. The reason for this is not made clear in the company submission but may reflect that the INO-VATE 1022 trial was open label, with no separate protocol for subsequent decisions regarding provision of HSCT. It may also reflect the decision by the company to include "*the total number of patients within the safety dataset that had an HSCT, regardless of their remission status, and regardless of their time of transplant and whether this was received prior to any post-induction therapy*" (CS, p185). The company justify this approach on the basis that it ensures "*that the economic model is reflective of what was observed within the trial, to avoid any potential misinterpretation of the outcomes*" (CS, p186). The company also consider that this approach is potentially conservative towards the benefit of inotuzumab, since a higher proportion of patients in the SoC arm received HSCT as a result of response to a subsequent induction treatment ([redacted] in the SoC arm and [redacted] in the inotuzumab arm).

The ERG has two main concerns arising from the current model structure and the use of HSCT data. Firstly, the ERG considers that the lack of an explicit link between CR/CRi and subsequent HSCT to be an important omission. Although the company employ covariate analysis within the parametric

survival modelling (see Section 5.2.6) to explore the impact of patient population characteristics (e.g. age, salvage status, prior SCT, duration of remission, Philadelphia chromosome and region), these covariates only alter the estimated survival predictions within each of the 3 main sub populations. As a result, the CR/CRi and HSCT outcomes (and hence the proportion of patients within each of the main initial health states) are derived from the overall population and are not related to specific patient characteristics and subgroups. However, since these characteristics will also potentially affect the CR/CRi and HSCT, the results of these covariate analyses were not considered by the ERG to appropriately estimate the survival of subgroups within the overall population.

Secondly, the decision to include any patient in the dataset who had an HSCT inevitably introduces additional heterogeneity. Hence, subsequent differences in survival between inotuzumab and SoC in this sub-population could be due to factors other than the treatment to which individuals were randomised. This is a particularly important aspect since the economic case being made by the company is based not only on attributing differences in the rates of CR/CRi and HSCT to inotuzumab but also to differences in the survival of patients who subsequently received HSCT.

5.2.6 Treatment effectiveness and extrapolation

The company's base case model makes use of three sets of parametric survival models (for each of the main health states/sub populations) combined with an additional assumption that individuals surviving more than three years post-HSCT would be 'cured' and return to the mortality risk for the general population.

The proportion of patients assumed to be in each of the 3 main health states from Cycle 1 was derived directly from the safety dataset from the INO-VATE 1022 trial and is reported in Table 9.

Table 9: Proportion of patient in each health state from Cycle 1

Health state	Inotuzumab	Standard of care
No CR/CRi & no HSCT	[redacted]	[redacted]
CR/CRi & no HSCT	[redacted]	[redacted]
HSCT & post-HSCT	[redacted]	[redacted]
Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant		

CS, Table 39 – p161

The use of the safety dataset (also referred to as the modified ITT dataset) excludes [redacted] of the 164 patients randomised to the investigator's choice arm. The company justified the exclusion of these

patients on the basis that this would limit any bias towards the inotuzumab arm, given that these SoC patients would be categorised as not achieving CR/CRi. The company also considers that removing these patients provides a more accurate representation of the efficacy of the SoC arm and provided detailed Kaplan-Meier data for each of the health states based on both the safety and ITT populations (see company response to clarification questions). The ERG considers that the use of the safety dataset appears appropriate for the purposes of the economic model and there appears no obvious bias in the subsequent OS and PFS estimates provided.

The rate of CR/CRi is determined only for those patients who did not progress to HSCT, and hence it differs from the remission outcomes discussed in Section 4.2.3. Patients in the *HSCT & Post HSCT* state are not distinguished according to whether they achieved CR/CRi. In response to points for clarification, the company provided more information about the breakdown by HSCT and CR/CRi status (see Table 6), but only for the ITT population, and hence the numbers corresponding to the safety population reported in this section were taken directly from the company model.

As previously noted, the model employs additional tunnel states to inform the period that patients wait for HSCT. The proportion of HSCT patients receiving HSCT in each cycle was derived from the respective arms of the INO-VATE 1022 trial and is summarised in Table 10. Clinical advice received by the company indicated that time to HSCT is shorter in UK clinical practice, with patients typically receiving HSCT by the third cycle. Hence, the company undertook additional scenario analyses to explore this issue by assuming a maximum of three cycles spent waiting for HSCT and using the average waiting time in the trial ([redacted] months for inotuzumab patients and [redacted] months for SoC patients on average, reflective of a maximum wait time of [redacted] and [redacted] model cycles in the two arms).

The ERG considers that the approach used in the base-case regarding the timing of HSCT to be consistent with company's decision to include "*the total number of patients within the safety dataset that had an HSCT, regardless of their remission status, and regardless of their time of transplant and whether this was received prior to any post-induction therapy*" (CS, p 185). The ERG does not consider it appropriate to model shorter waiting times as the focus of the model is on any HSCT received as opposed to those that were received as a direct result of the initial induction therapies.

Table 10: Proportion of HSCT patients receiving HSCT in each cycle

Cycle	Inotuzumab arm	SoC arm
1	[redacted]	[redacted]
2	[redacted]	[redacted]

3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
Total	**100.00%**	**100.00%**

CS, Table 40 – p162

OS and PFS outcomes were estimated using a series of covariate-adjusted parametric survival models estimated separately for each health state. The company notes (CS, p173) that there were two definitions of PFS employed in the trial. Within the model, the company uses the more extensive definition of PFS which includes not only the time from randomisation to the first documentation of objective disease progression or due to death, but also disease progression incorporating relapse from CR/CRi, and treatment discontinuation due to the global deterioration of health status. The company justified the use of the broader definition of PFS as being more relevant to clinical practice in ALL. The ERG considers this reasonable.

Separate parametric models were fitted to data from the INO-VATE 1022 trial (safety dataset) for each of the three main states/subpopulations *No CR/CRi & no HSCT, CR/CRi & no HSCT, HSCT & Post HSCT*. Parametric models for the *No CR/CRi & no HSCT, CR/CRi & no HSCT* states were fitted using the date of randomisation as the baseline. Parametric models for the *HSCT & Post HSCT* state were fitted using a baseline of the date of HSCT, since time to receipt of HSCT is already captured by the tunnel states. However, as the trial definition of PFS includes proceeding to HSCT without having achieved CR/CRi, this means that some of the patients in the *HCST & Post HSCT* state would have been classed as progressed prior to HCST for the trial analysis, but not in the company model,

which estimates time to progression after HSCT. The ERG considers that this is reasonable given the structural assumptions regarding HCST in the decision model.

A series of covariates were employed within the parametric models to capture treatment related differences and to explore the impact of different prognostic factors. A summary of the covariates and justification provided by the company are reported in Table 11. The covariates were stated to have been validated by UK clinicians.

Table 11: Covariates included in the parametric models and justification

Covariate	Justification
Treatment	Treatment covariates were incorporated within the model to allow the shape and scale parameters to vary in accordance to the specific treatment data
Age group (<55/≥55)	This was a stratification factor in the INO-VATE 1022 trial
Duration of first remission at randomisation IVRS (< 12 months, ≥ 12 months)	This was a stratification factor in the INO-VATE 1022 trial
Salvage status (1/2) IVRS	This was a stratification factor in the INO-VATE 1022 trial
Philadelphia category (Ph+/-)	Given the importance of Ph status for prognosis, the parametric models included this covariate to explore the performance of inotuzumab versus SoC within the population
Prior HSCT (Yes/No)	Included to be in line with current UK clinical practice where a 2nd SCT is not reimbursed. Also, in current clinical practice, FLAG-IDA would be prescribed for patients with the aim of bringing them to SCT. A patient with a prior SCT, would therefore not be treated with FLAG-IDA, as a second SCT would not be reimbursed.
Region (EU, North America, Japan and Other Asia)	Treatment in Japanese patients were seen as an outlier from other countries, with regard to the typical conditioning regimens available (such as ThioTEPA associated with an increase in the incidence of VOD), and therefore was incorporated as a covariate to explore its impact on the predicted cost-effectiveness outcomes.
Key: HSCT, haematopoietic stem cell transplant; IVRA, interactive voice response system; Ph+/-, Philadelphia chromosome positive/negative; SoC, standard of care; VOD, veno-occlusive liver disease.	

CS, Table 45 – p172

Parametric survival curves were fitted to the empirical Kaplan-Meier data on PFS and OS to extrapolate outcomes beyond the trial follow-up period. The company considered several different survival models for the curve fit: generalised gamma, exponential, Weibull, Gompertz, log-logistic and log-normal. The choice of parametric curve was stated to be informed through visual inspection, assessment of clinical plausibility, and metrics of statistical fit in line with NICE Decision Support Unit guidelines. Since treatment was included as a covariate, the same parametric curves were applied to both treatment arms for OS and PFS.

Table 12 summarises the choice of parametric curve for each health state along with the main justification provided by the company. Full details of the company approach and justifications for each individual health state are provided in the CS (CS, p170-191). The ERG does not consider it appropriate to replicate the information reported by the company for each state. Instead, the ERG discusses the appropriateness of the general approach used and focuses on the approaches and assumptions applied to the *HSCT & Post HSCT* state (since 95% of the predicted QALY gain is attributed to this health state).

Table 12: Summary of company justification for selected parametric curves

Health state		Parametric curve	Goodness of visual fit	Best statistical fit	Clinically plausible
No CR/CRi & no HSCT	OS	Log-logistic	Yes	No	Yes
	PFS	Log-logistic	Yes	Yes	Yes
CR/CRi & no HSCT	OS	Log-logistic	Yes	Yes	Yes
	PFS	Log-normal	Yes	Yes	Yes
HSCT & Post-HSCT	OS	Gompertz	Yes	Yes	Yes
	PFS	Gompertz	Yes	No	Yes

The ERG regard the splitting of the INO-VATE 1022 trial into three health states (or sub-populations) and the fitting of multiple parametric survival curves to be an overly complex approach to extrapolation compared to making more use of the observed Kaplan-Meier data. Overall survival is complete for the *No CR/CRi & no HSCT* state, and hence extrapolation and the fitting of parametric survival models for PFS and OS are unnecessary. In the *CR/CRi and no HSCT* state, the Kaplan-Meier data for OS extends to [redacted] years and [redacted] survival probability on the inotuzumab arm and [redacted] years with [redacted] survival probability on the standard of care arm. The Kaplan-Meier data for the *HSCT & post HSCT* sub population extends to [redacted] and [redacted] years respectively for inotuzumab and SoC. Indeed, it is possible that with the further data cut that was reported to be available in April 2017 that there will be no need for any extrapolation in the *CR/CRi and no HSCT* state and that the *HSCT & post HCST* Kaplan-Meier data could extend past three years (i.e. the cure point assumed in the base-case).

The company approach to modelling survival addresses several different issues:

(i) potential non-proportionality of hazards between control and treatment group (particularly in the *HSCT & Post HSCT* state);

(ii) differences in treatment and patient characteristics which may impact on survival estimates, and;

(iii) difference in the time origin for the separate health state (i.e. from the point of randomisation for the *CR/CRi & no HSCT* and *No CR/CRi & no HSCT* states and from receipt of HSCT for the *HSCT & Post HSCT* state).

When proportional hazards (PH) can be considered an appropriate assumption, the typical approach is to model the effect of treatment on the scale of the parametric survival distribution. In situations where PH does not appear appropriate, there are several alternative methods which are conventionally used including: the use of accelerated failure time approaches (AFT); piece-wise survival models (i.e. assuming that PH holds within specific time intervals); stratified proportional hazard models (i.e. assuming PH holds within specific subgroups or strata but not across these) and fitting independent (i.e. fully stratified) survival curves. The method used by the company does not follow any of these more conventional alternatives. Instead, the company proposes an alternative approach based on the following assumptions:

- The survivor function (OS and PFS) is assumed to follow a specific underlying distribution (e.g. exponential, Weibull, gompertz, log-logistic etc).
- The survivor functions for inotuzumab and SoC are assumed to follow the same underlying distribution.
- The scale parameter of these distributions is a function of individual characteristics (e.g. age, region, Ph status, salvage, region etc) and treatment (inotuzumab or Soc).
- The shape parameter depends only on treatment with inotuzumab (i.e. whether the hazard function is constant, increasing or decreasing with time depends only on treatment with inotuzumab).

The key issues identified by the ERG were the use of treatment covariate on the scale parameter and a separate covariate (inotuzumab only) applied to the shape parameter. The ERG considered this approach to be unconventional, incorporating elements from both a more conventional stratified PH model (i.e. by incorporating a treatment covariate on the scale parameter) as well as independent (or fully-stratified) survival curve fitting (i.e. by allowing a different shape of the hazard function for the different treatments). The ERG requested further clarification and justification from the company regarding the appropriateness of this method compared to more conventional alternatives.

The company response to the ERG clarification stated that:

"The parametric curve methods used for modelling OS and PFS for each of the three patient groups (No CR/CRi & no HSCT, CR/CRi & no HSCT and SCT & Post-HSCT) are more flexible than

standard models which typically include one treatment effect (i.e., models that assume proportional hazards or constant treatment effect for the accelerated failure time model distributions).The additional flexibility of model fits in our analyses comes from the fact that treatment can affect two distributional parameters rather than one (e.g., for Weibull, this would be shape and scale rather than just scale). The models, however, cannot be characterised as "fully-stratified", as they not rely on separate datasets by treatment group.

By allowing treatment to affect two parameters, this enables a form of stratification by treatment, while maintaining a common effect for the remaining covariates in the model. Although this does require an assumption of proportionality for each covariate, it importantly allows the effect of these covariates to be consistent, regardless of treatment group. This is clinically appealing, as well as technically important, because we must properly control for the fact that the analyses split by the three patient groups are no longer a strictly randomised comparisons)."

These models were fit using R, specifically the 'flexsurv' package (Jackson 2016). The guidance for 'flexsurv' gives an example for the case of a generalised gamma curve, which allows an ancillary parameter (such as 'shape') to depend on the treatment covariate, providing 'a model with a time-dependent effect that is neither proportional hazards (PH) nor accelerated failure time (AFT)' (Jackson 2016).

In comparison to the current approach of partial stratification, fitting fully stratified models for each treatment reduces sample size, and can lead to convergence issues, due to the splitting of the data into the various patient groups. By way of example, fitting curves to post-SCT PFS would lead to curves fitted to a set of [redacted] patients ([redacted] events) in the Investigators Choice (SoC) arm.

As requested, differences between model fits were investigated for: fully stratified curves; curves where all covariates inform 2 distributional parameters (e.g. shape and scale for Weibull); and curves (as are used within the model) which are partially stratified (that is, in which only the treatment covariate affects the two parameters). Both additional types of model have been fitted to the curves chosen as the base case for OS and PFS; from these, AIC and BIC values were compared for each patient group.

The results of these comparisons show that the method we have selected provides statistically better model fits (via AIC and BIC) compared to these two alternative methods in all but one instance (with the exception being the HSCT group for PFS, for which data are scarce.). This provides additional support for the choice of parametric survival modelling within the submission."

Response to clarifications, Question B5 p1-2

The ERG acknowledges the points made within the clarification and the provision of additional data supporting the statistical fit assumptions. In this response it is not clear why the company report only one AIC and BIC value for the stratified analysis if this was achieved by fitting two separate models. However, the ERG remains concerned with the general approach which it considers introduces potentially unnecessary complexity and assumptions. Given the completeness/near-completeness of the Kaplan-Meier data for two of the states (*CR/CRi & no HSCT* and *No CR/CRi & no HSCT*), the additional advantages conferred by parametric modelling approaches appear to be largely confined to the *HSCT & Post HSCT* state, facilitating extrapolation beyond the observed data and exploration of the impact of alternative cure time points.

While the ERG acknowledges the additional flexibility conferred by the novel approach employed by the company, the ERG is particularly concerned with the assumption that the shape parameter depends only on treatment with inotuzumab. To illustrate the ERG's specific concerns, Figure 4 provides a graphical summary of the hazard function assumed for inotuzumab and SoC for OS based on the survival distribution chosen in the base case (Gompertz) for the *HSCT & Post HSCT* state.

Figure 4: Hazard function for OS (Gompertz) in the HSCT & Post HSCT state

Hence, although the same underlying (Gompertz) distribution is applied to both inotuzumab and SoC, the inclusion of a separate covariate on the shape parameter for inotuzumab results in fundamentally different hazard functions emerging over time. That is, while the hazard of mortality is increasing with time for SoC patients in the *HSCT & Post HSCT* state, this hazard is decreasing for patients in the inotuzumab group. While this may appropriately reflect the hazard functions over the duration of the trial, it is uncertain whether this provides an appropriate basis for subsequent extrapolation.

It is also evident from Figure 4 that the hazard with inotuzumab appears to be converging towards 0. The different shapes of the hazard functions appear to suggest 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 for SoC patients who received HSCT. The ERG does not consider that such a strong assumption is adequately supported by the existing data and neither does this assumption appear clinically plausible. The Kaplan-Meier data for OS for patients in the *HSCT & Post HSCT* state, from a baseline of the date of HSCT, is shown in Figure 5. The associated parametric functions (up to 3 years, after which patients are assumed to be cured) are shown in Figure 6.

Figure 5: Kaplan-Meier OS data for HSCT & Post-HSCT patients – safety population

Response to ERG clarifications, Figure 11 – Question B1 p66

Figure 6: Kaplan-Meier and parametric OS curves for HSCT & Post-HSCT patients – safety population

CS, see Excel® model

It is evident from both figures that the additional mortality benefits assumed for inotuzumab within the *HSCT & Post HSCT* state are driven by differences in the observed data which subsequently arise at approximately [redacted] months post HSCT after the Kaplan-Meier curves cross. The ERG considers that these differences are highly uncertain given the small number of patients still at risk beyond this time point (number at risk; SoC [redacted], inotuzumab [redacted]).

During clarification the ERG requested estimates of restricted mean survival time (RMST) for each state. The company response included RMST for those with CR/CRi and no HSCT and for two different sub populations compared to those included in the model: patients that did not achieve CR/CRi, including those that went on to have HSCT; and patients with CR/CRi and HSCT (see Table 13). [redacted]

Table 13: RMST for OS in the HSCT & Post-HSCT state for patients who achieved CR/CRi

[redacted]

[a] If the minimum of maximum OS time observed in each of the two arms (i.e., minimax) was < the planned truncation time, then the analysis was actually done based on the minimax as the truncation time.

Response to ERG clarifications, Table 6 – Question B6 p5-6

The ERG considers that significant uncertainty exists surrounding the assumptions of additional mortality benefit within the *HSCT & Post-HSCT* state and that the parametric modelling further increases this uncertainty, even over relatively short periods of extrapolation.

Figure 6 clearly illustrates the impact of assuming continuing divergence based on the parametric modelling assumptions arising between the end of the Kaplan-Meier data ([redacted] and the start of the separate cure assumption (36 months). Importantly, the difference in the proportion of patients reported to be still alive between inotuzumab and SoC at 36 months is higher than that reported at the end of the Kaplan-Meier data.

The same issues with the analysis of OS also apply to the analysis of PFS. The Kaplan-Meier data for *HSCT & Post HSCT* patients in the safety population show a similar pattern to the OS, as shown in [redacted]. The Kaplan-Meier curves cross at around [redacted] months, when only [redacted] patients in the inotuzumab arm and [redacted] on standard of care remain at risk (company response to clarification Figure 9). At the final Kaplan-Meier data point on the standard of care arm, there is a difference in PFS of [redacted] between treatment arms. However, the parametric survival curves continue to diverge, with effectively [redacted] on standard of care assumed to progress, while the curve for inotuzumab plateaus at around [redacted] PFS.

Figure 7: Kaplan-Meier data and PFS for HCST & post HSCT patients - safety population

The ERG does not consider the assumptions employed in the parametric modelling approach applied in the company base-case for the *HSCT & Post HSCT* state are robustly supported by the existing data. The ERG also has concerns regarding the clinical plausibility and external validity of the extrapolated results for this state. A recently published international reference analysis of outcomes in adults with R/R Ph-negative ALL patients[2] reported survival data based on 1,706 patients (including 1,416 patients with information on HSCT status). Overall survival at 36-months was reported to be 11% in the overall population (including patients who did and did not receive HSCT) and exceeded 20% in patients who received HSCT following first salvage treatment. These appear higher than the predicted survival rate of [redacted] for SoC patients in the *HSCT & Post HSCT* state within the economic model. Furthermore, the shape of the OS curve reported within the international reference analysis study for patients following receipt of HSCT after conventional chemotherapy clearly showed that the hazard of mortality was decreasing (as opposed to increasing) with time.

The uncertainties surrounding the assumptions of additional mortality benefit within the HSCT & post-HSCT state are acknowledged in the company submission and in their subsequent response to clarification questions from the ERG. Regarding the results of the additional RMST analyses provided for the HSCT & Post-HSCT state, the company states that [redacted] (Company response to ERG clarification question B6).

Given these uncertainties the ERG also requested that the company provide a separate scenario analysis based on pooling the overall survival for the *HSCT & Post-HSCT* state. Although the company provided the requested scenario, they stated that:

"Although pooling the data creates a larger evidence which can be used to inform post-HSCT survival, doing so fails to account for prognostic factors associated with overall survival that may differ by treatment, for example MRD negativity. Therefore pooling survival post-transplant should be interpreted with extreme caution as we believe that they are neither appropriate nor clinically plausible and will lead to an extremely biased estimate of cost effectiveness"; and

"*Pooling the data fails to account for prognostic factors associated with overall survival that may differ by treatment. Furthermore, pooling also abandons the available randomised, controlled evidence past the point of transplantation*".

Response to ERG clarifications, Questions B3&B4 - p74-75

The ERG does not agree with either statement. While an additional mortality effect of inotuzumab in the *HSCT & Post-HSCT* state is clinically plausible (see later discussion on MRD outcomes), the current data does not appear to robustly support this effect or the assumptions employed within the base-case analysis. Furthermore, the ERG considers that the current parametric model for the *HSCT & Post HSCT* state already abandons the available randomised evidence by being based on a non-randomised subgroup and relying on survival data estimates subsequent to the point of randomisation.

Despite these concerns the ERG acknowledges that the assumption of differences in the PFS and OS estimates within the *HSCT & post-HSCT* state remains clinically plausible. One potential justification identified by the company in their initial submission and reinforced during the clarification stage concerns the statistically higher rate of MRD-negativity for inotuzumab patients receiving HSCT versus SoC ([redacted] vs [redacted]). While MRD status was not a primary outcome in the INO-VATE 1022 study, the company considered that since MRD status has previously been found to be an important prognostic factor in determining a patients' long-term survival, the difference in MRD-negativity rates lends additional support to the assumed outcome differences incorporated within the base-case model. It is not clear from the CS why, if MRD status is considered to be an important prognostic factor, it was not considered as a covariate in all parametric models, including the company base case analyses.

The results of an exploratory MRD analysis was reported in Appendix 7 of the CS based on pooling data in both arms for the sub population HSCT & Post-HSCT and including a separate covariate for

MRD status (on both the shape and the scale parameters). In this manner the prognostic value of MRD is estimated based on a post randomisation sub population of the INO-VATE 1022 trial. The cost-effectiveness results based on this alternative and exploratory analysis was presented as a separate scenario within the initial CS.

The ERG considers that the exploratory analysis based on MRD status, while highly uncertain, appears more clinically justifiable as a basis for extrapolation than the approach employed in the base-case and importantly provides projections for the *HSCT & Post HSCT* state for SoC patients that appear to have greater external validity.

5.2.6.1 Mortality beyond the trial follow-up

As previously noted, a further assumption was made concerning the extrapolation of OS patients in *HSCT & Post HSCT* state. At a specific time point (3 years in the base-case), surviving patients in the *HSCT & Post HSCT* state are assumed to be cured (irrespective of whether their initial treatment was inotozumab or SoC) and hence face no risk of further relapse at any point in the future. Within the model this assumption is implemented by assuming that the mortality risk beyond the cure point is the same as that of the general population (age and gender matched to the patient population characteristics in the INO-VATE 1022 trial), while accounting for potential morbidities affecting HRQoL.

The ERG has a number of important concerns regarding the choice of the cure time point and the assumption than surviving HSCT patients will subsequently revert to the mortality risk of the general population. Firstly, this assumption inevitably means that the survival gains estimated at 3 years are effectively extrapolated over a lifetime. This will inevitably have a significant impact on the resulting estimates of cost-effectiveness. This is clearly illustrated in Figure 8 and Figure 9which show the projected difference in PFS and OS over the entire 60-year time horizon.

The ERG notes that the slightly different shapes of the PFS and OS curves is explained by the assumption that PFS is assumed to remain stable post HSCT but needs to be capped within the model by OS to ensure that there can never be more patients in PFS than alive. The majority of the differences in PFS, OS and hence QALYs are derived after the follow-up period of the trial. The ERG considers this a strong assumption since the long-term consequences of therapy in this patient population are unknown.

Figure 8: PFS differences projected over the lifetime horizon

CS, Figure 45 – p194

Figure 9: OS differences projected over the lifetime horizon

CS, Figure 46 – p173

Secondly, the choice of cure point is important since it means that the survival gains observed at that chosen time point are those that are then extrapolated over an entire lifetime. This should therefore have a significant impact on the resulting estimates of cost-effectiveness. The company noted that previous economic models of other therapies in similar therapeutic areas has used an estimate of the

cure point up to 5 years and that their clinical advisors considered a range between 2 and 5 years to be clinically appropriate.

The company subsequently explored alternative cure points across the range 2 to 5 years and considered the clinical validity of subsequent predictions of post-HSCT survival based on the chosen survival distribution (Gompertz). The company noted that using later cure points (4 to 5 years) appeared to result in predictions for survival post HSCT in the SoC which were not considered clinically plausible ([redacted] of patients in the SoC were predicted to be alive at 5 years). The use of an earlier cut point at 2 years was considered too conservative to inotuzumab (with predictions of [redacted] and [redacted] of patients alive post HSCT for inotuzumab and SoC, respectively). The company concluded that the use of a 3 year cut point appeared most clinically plausible (with predictions of [redacted] and [redacted] of patients alive post HSCT for inotuzumab and SoC, respectively) and potentially conservative towards inotuzumab. Additional clinical advice received by the company supported this choice based on the visual assessments and clinical plausibility of the estimates for SoC.

The ERG considers that the choice of a specific cure point is an important source of uncertainty within the current model. The ERG is concerned that the justification for the 3 year point assumed in the base-case appears largely determined on the basis of the clinical plausibility of the survival projections based on the parametric modelling approach as opposed to reflecting the most clinically appropriate point. The ERG has previously noted potential concerns regarding the clinical validity of the parametric modelling approach applied to the *HSCT & Post HSCT* state and hence does not consider this an appropriate basis to inform the choice of cut point.

Based on a visual assessment of the overall survival curves and on post HSCT survival reported in the international reference study by Gokbuget et al[2] (which used a sample of 1,337 patients with HSCT after 1st salvage treatment with follow up reported up to a maximum of approx. 4 years), the ERG considers that a cut point of 3 years could be potentially optimistic since a small number of further mortality events are reported beyond 36 months. However, due to the issues noted by the company and the ERG concerning the clinical validity of projections based on later cut points, the ERG advises caution in interpreting the scenario results.

A further concern relates to the structural 'cure' assumption itself and specifically the assumption that patients revert back to general population mortality rates. The ERG acknowledges that this is a common assumption applied within existing models in the general area but considers that this assumption is subject to significant uncertainty. The ERG notes that several clinical studies have

more formally assessed the long term survival after allogeneic HSCT which appear to have consistently reported lower long-term survival compared to the general population.[14-17]

During the clarification stage the ERG requested that the company provide additional clinical evidence to support the cure assumptions and to discuss the generalisability of the findings from existing studies which suggest ongoing mortality differences compared to the general population. In their response, the company highlighted that the studies cited by the ERG were conducted on historical patient cohorts and hence were likely to overestimate the mortality rates in current clinical practice.

The company also presented a threshold analysis which identified the maximum relative risk at which inotuzumab would remain cost-effective at a threshold of £50,000 per QALY in the base-case analysis. The company noted that the relative risk of mortality post HSCT would have to be 3.126 higher compared to the general population for the incremental cost-effectiveness ratio (ICER) to exceed the £50,000 threshold. The company considered that this value appeared large given the curative intention of HSCT and concluded that any plausible adjustment to the mortality rate should be minimal.

Figure 10: Company threshold analysis on relative risk applied to general population mortality

Response to ERG clarifications, Figure 25 – Question B7 (iii) p82

The ERG considers that there remains significant uncertainty surrounding the longer-term survival of post HSCT patients. For example, the study by Martin et al (2011) concluded that while "mortality

rates improve dramatically during the first 5 years after HCT" they "remain four to nine-fold higher than the general population for at least 25 years thereafter".[16] The ERG acknowledges that many of the studies are derived from historic cohorts and hence may over-estimate mortality compared to current practice. However, significant concerns persist regarding the late effects of HSCT and have led to recent initiatives to improve longer term outcomes.[18]

5.2.7 Health related quality of life

The pivotal clinical trial INO-VATE 1022 collected HRQoL evidence from trial participants using both the EORTC QLQ-C30 and EQ-5D. The company also undertook a separate systematic literature search and review of utility studies which reported relevant health-state values.

The CS described the search strategies used to identify relevant studies of utility values/HRQL associated with R/R ALL. The search strategies were briefly described in the main body of the submission and full details were provided in Appendix 8.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the National Health Service Economic Evaluations database [NHS EED], and the Health Technology Assessment Database [HTAD]) were searched on 6 September 2016. The search strategies used for each database were reported in Appendix 8 of the CS.

The company reported on page 199 of the CS that the same databases, HTA websites and conference proceedings were searched as for the cost-effectiveness review.

The structure of the search strategies for MEDLINE and EMBASE were appropriate. Disease terms for RR B-cell ALL were combined with a set of search terms for utility or quality of life and limited to English language. The searches of MEDLINE In Process, EconLit and the Cochrane Library were also appropriately structured, using disease terms only. The MEDLINE In Process search contained a limit to studies not already in MEDLINE.

The strategies contained relevant subject headings, text word searches and synonyms and all search lines were combined correctly. A possible typing error was identified in the search strategies: lympholeuci* could have been more appropriately truncated as lympholeuc*. In the search of MEDLINE In Process a lack of truncation was noted which would have affected the sensitivity of this search, however truncation was used appropriately in the other databases searched.

The methods used to search for studies via conference proceedings and websites were not provided by the company in the submission nor in their response to ERG's points for clarification. Therefore, although the conference proceedings sources and websites searched were appropriate, it is not possible to assess the methods used to search these sources.

The systematic search identified seven studies which were included in the utility/health-related quality of life review comprising six journal articles and one HTA (CS, Table 55). Utilities derived from the INO-VATE 1022 trial were subsequently compared with those identified in the literature and a quality assessment of the included studies was carried out using a checklist[19] (CS, Appendix 8.4).

Table 14 provides a summary of the utility values used within the model, including the source and justification.

Table 14: Summary of utility values applied in the model

State		Utility value: mean (standard error)	95% confidence interval	Justification
Baseline		InO: 0.69 (0.02) SoC: 0.67 (0.03) Pooled: 0.69 (0.02)	0.65–0.74 0.62–0.73	Assumed baseline utilities collected in INO-VATE 1022 represent the baseline patient population before treatment.
No CR/CRi & no HSCT		[redacted]	[redacted]	Assumed the end of treatment utility from INO-VATE 1022 represents HRQL in this health state.
CR/CRi & no HSCT		[redacted]	[redacted]	Assumed the end of treatment utility from INO-VATE 1022 represents HRQL in this health state.
Post-HSCT	<1 year post	0.59 (0.10)	0.40–0.78	Assumed that AML utilities after HSCT from Kurosawa et al. (2016) can be applied to R/R ALL patients. These include the disutility for GvHD.
	1–2 years' post	0.75 (0.03)	0.69–0.82	
	3–5 years' post	0.74 (0.02)	0.70–0.78	
	>5 years post	0.76 (0.03)	0.71–0.81	
Progression		0.30 (0.04)	0.22–0.38	Taken from the study by Aristides et al. (2015).(Aristides, Barlev et al. 2015)
VOD after HSCT applied for one cycle		0.208	NA	Assumed to be approximately the same

			as acute liver failure pre-transplant. (SMC). This is a conservative approach, as reasons described above.
Key: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CR, complete remission; CRi, complete response with incomplete count recovery; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; InO, inotuzumab ozogamicin; NA, not applicable; SoC, standard of care; VOD, veno-occlusive disease.			

CS, Table 58 – p214

HRQoL utility values were assigned to each of the three main health states, the progression sub-state and to the incidence of VOD. The company assumed that the impact of adverse effects (excluding VOD) would already be accounted for within the utility values reported in the INO-VATE 1022 trial.

The model uses treatment specific EQ-5D utilities (using a UK value set) for the *No CR/CRi & no HSCT* and *CR/CRi & no HSCT* states derived from INO-VATE 1022. The use of pooled utility values was explored in a separate scenario analysis. The company reported that the values used for these states were similar to those reported within the studies identified by the SLR.

In the absence of relevant data from INO-VATE 1022, the utility values assigned to the progression state were derived from the systematic literature review. The review did not identify any relevant utility estimates to inform the *HSCT & Post HSCT* or the impact of VOD. The utility values were subsequently sourced from published decision models and cost-effectiveness studies.

The utility estimate applied to patients in the progression state in the model was 0.3. This was based on a study by Aristides' et al which used a representative sample of the general population (n=123) and a time trade-off approach to generate utility values for a variety of health states related to adult relapsed or refractory B-precursor ALL.[20] In the company base case this value is applied to the progression state for all three sub-populations. This means that in the company model progression is assumed to influence health related quality of life but does not impact on estimated survival. Patients who survive beyond the 'cure' point post HSCT, but who have progressed, experience general population mortality rates but with a health related quality of life of 0.3. The utility value used for the progressed disease state has a large impact on the estimated QALY gains, as the model predicts progression in [redacted] of patients who receive HSCT following standard of care and [redacted] of patients receiving HSCT following inotuzumab.

Utility values for the *HSCT & Post-HSCT* health state were derived from a published decision model comparing allogeneic HSCT versus chemotherapy in acute myeloid leukaemia (AML).[21] The utility values from this study appear to be based on EQ-5D values derived using Japanese value sets. Although these values are derived from a separate population, clinical advisors to the company considered it appropriate to assume that these could be applied to the ALL population.

Utilities for HSCT applied into the model are as follows: for less than 1 year post HSCT (0.59), 1–2 years post-HSCT (0.75), 3 to 5 years post-HSCT (0.74) and 5 years post-HSCT (0.76), until death. In the company base case these are only applied to those who remain progression free post HSCT. The company provide a scenario analysis in which these utilities are applied to all patients, regardless of progression status, but note that this assumes that progression post HSCT is not a relevant consideration for patient's quality of life. The company noted that the utility values for HSCT beyond the cure point assumed in the model were lower than the equivalent general population utility values based on a similar age. The company considered that applying lower values than that reported for the general population beyond the cure point was potentially conservative towards inotuzumab.

In the absence of VOD specific estimates, the company made an assumption that the HRQoL of VOD would be similar to that reported for acute liver failure prior to a transplant (0.208) and would last for a single 28-day cycle.

The ERG considers that the company have made a significant effort to source relevant estimates and that the sources included within the model reflect the best available evidence. The review itself was transparent and well conducted. Although the ERG notes that several assumptions were subsequently required, these were considered reasonable and the company sought to validate these with clinical advisors.

The ERG considers that the open-label design of INO-VATE 1022 inevitably introduces potential bias for subjective endpoints such as HRQoL. Given this potential bias, the ERG considers that the use of pooled utility values reported within a separate scenario may be more appropriate than assuming treatment related differences in utilities. However, the ERG notes that this is only relevant to the *No CR/CRi & no HSCT* state and that differences within this state are not a key driver of cost-effectiveness.

The ERG does not agree that the continued use of post HSCT utility estimates, as opposed to switching to general population EQ-5D estimates, beyond the cure point is conservative. As previously highlighted, existing epidemiological data indicates that surviving HSCT patients continue

to experience higher mortality and morbidity for a sustained period, relative to the general population. Furthermore, although the post-HSCT utility values applied in the model are lower than those reported for the general population, the comparison presented by the company relates to a specific time point. When utility values are considered over the 60-year lifetime horizon then it is evident that the utility values assigned to the *HSCT & post HSCT* state may eventually exceed general population utility estimates, which naturally decline with age. The ERG thus considers that utilities in the *HSCT & Post HSCT* state should be further adjusted for age as reported within a separate scenario by the company (in line with NICE Guide to the methods of technology appraisal 2013: CS, Table 83).

5.2.8 Resources and costs

The CS provided a detailed description of resource use and cost. These included: drug acquisition costs, drug administration costs, concomitant medication and monitoring costs, and costs related to the health states and adverse events.

To identify cost and resource use data to inform the assessment of cost-effectiveness, the company performed a systematic review of the literature for R/R B-bell ALL patients. The CS described the search strategies used to identify relevant healthcare resource utilisation and cost studies related to R/R ALL. The search strategies were briefly described in the main body of the submission and full details were provided in Appendix 9.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the National Health Service Economic Evaluations database [NHS EED], and the Health Technology Assessment Database [HTAD]) were searched on 6 September 2016. The search strategies used for each database were reported in Appendix 9 of the CS.

The company reported on page 215 of the CS that the same databases, HTA websites and conference proceedings were searched as for the cost-effectiveness review.

The basic structure of the search strategies for MEDLINE and EMBASE were appropriate. Disease terms for RR B-cell ALL were combined with a set of search terms for costs or resource use and results were limited to English language. The searches of MEDLINE In Process, EconLit and the Cochrane Library were also appropriately structured, using disease terms only. The MEDLINE In Process search contained a limit to studies not already in MEDLINE. A date limit of studies published from 2000 onwards was applied to the searches of MEDLINE, EMBASE and EconLit.

The strategies contained relevant subject headings, text word searches and synonyms for RR B-cell ALL and costs or resource use. All of the search lines were combined correctly. A possible typing error was identified in the search strategies: lympholeuci* would have been more appropriately truncated as lympholeuc*. In the search of MEDLINE In Process a lack of truncation was noted which would have affected the sensitivity of this search, however truncation was used appropriately in the other databases searched.

The search strategies for MEDLINE, EMBASE and the Cochrane Library contain a set of terms to limit the results to UK studies. However, a fairly narrow range of textwords for the UK is used. Further synonyms could have been included to improve the sensitivity of this search, for example GB, "G.B.", "U.K." and also the inclusion of the countries that make up the UK and major UK cities.

The methods used to search for studies via conference proceedings and websites were not provided by the company in the submission nor in their response to ERG's points for clarification. Therefore, although the conference proceedings sources and websites searched were appropriate, it is not possible to assess the methods used to search these sources.

Eleven studies met the inclusion criteria of this review reporting a variety of cost valuations or health resource use consumption, which are presented in Table 60 of the CS.

5.2.8.1 Drug acquisition costs

For the treatment costs applied in the model, the average number of vials required per cycle was calculated using an approach based on 'method of moments'. By fitting a lognormal distribution to body surface area, the relative frequency of the dose and number of vials required was estimated. The ERG remains unsure why this approach was necessary for inotuzumab given that information of the actual administered dosage and number of vials used within the INO-VATE 1022 trial was presumably available to the company. However, the ERG does not consider that this approach would necessarily introduce any important bias and considers the method of moments approach to be an appropriate approach more generally to appropriately estimate vial usage. Dosages for drugs not included in the trial (idarubicin and imatinib) were obtained from their SPCs.

Table 15 summarises the unit costs, average drug usage and number of patients per treatment cycle in the model.

Table 15: Dosage and cost estimates

Drug (Vial size)	Cost per unit (source)	Mean actual dose by cycle	Average vials required using MoM	Number of patients per cycle	Total vials
InO (1mg vial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fludarabine (50mg vial)	£0.47/mg (eMit)	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine - FLAG (1g/10ml vial)	£0.06/mg/ml (eMit)	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine – CM (100mg)	£0.06/mg/ml (eMit)	[redacted]	[redacted]	[redacted]	[redacted]
High dose cytarabine (1g/10ml vial)	£0.06/mg/ml (eMit)	[redacted]	[redacted]	[redacted]	[redacted]
G-CSF (300µg/1ml)	£0.18/µg/ml (MIMS)	[redacted]	[redacted]	[redacted]	[redacted]
Mitoxantrone (20mg/10mm)	£15.76/mg/ml (eMit)	[redacted]	[redacted]	[redacted]	[redacted]
Idarubicin (5mg vial)	£17.47/mg (MIMS)	[redacted]	[redacted]	[redacted]	[redacted]
TKI – Imatinib (100mg tablet)	£0.16/mg (MIMS)	[redacted]	[redacted]	[redacted]	[redacted]

CS, Table 63 – p227

Inotuzumab and SoC regimens were administered to patients up to a maximum of 6 and 4 cycles, respectively. The median number of treatment cycles was three cycles for inotuzumab and one for the SoC arm. The total drug acquisition costs of inotuzumab were calculated based on the cost per vial

([redacted]) multiplied by the estimated number of vials received within the trial ([redacted]). For the SoC arm, the total cost of treatment was based on a weighted average of the proportion of patients from the INO-VATE 1022 trial who received each SoC combination therapy (FLAG-IDA, CM, HIDAC or concomitant imatinib for Ph+ patients). Idarubicin (IDA) was costed in the model base case (with efficacy of FLAG used as a proxy for FLAG-IDA) justified on the basis that FLAG-IDA is the standard treatment for R/R B-cell ALL patients in the UK. The cost estimates assumed that patients received only whole vials and there was no vial sharing.

Table 16 presents the mean total acquisition costs for each treatment arm. The total cost per treatment was applied as a lump sum in Cycle 0 for all patients. Alternative scenarios provided by the company explored the cost-effectiveness results when inotuzumab is applied for only three cycles (while keeping the efficacy unchanged) and applying the cost of FLAG only (omitting idarubicin) in line with the INO-VATE 1022 trial (CS, Table 82).

Table 16: Drug acquisition costs

Drug		**Total cost**		
Inotuzumab		[redacted]		
Drug		**Cost**	**Proportion of patients**	**Total cost**
Standard of care	FLAG-IDA	[redacted]	[redacted]	[redacted]
	CM	[redacted]	[redacted]	
	HIDAC	[redacted]	[redacted]	
	TKI (Imatinib) Ph+ patients only	[redacted]	[redacted]	

Key: CM, cytarabine plus mitoxantrone; FLAG, fludarabine, cytarabine, granulocyte-colony stimulating factor; HIDAC, high dose cytarabine; IDA, idurabicin; InO, inotuzumab ozogamicin; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia chromosome positive.

CS, Table 65 – p230

Patients in the INO-VATE 1022 trial received subsequent induction treatments. The proportion of patients who receive each subsequent induction treatment in the model was taken directly from the INO-VATE 1022 trial. As these subsequent induction treatments may have impacted OS, the company claims that including the costs of these treatments in the model minimises any bias.

Details of the subsequent treatments received for both arms of INO-VATE 1022 are reported within the company submission (CS, Table 70). The company subsequently excluded some treatment costs (specifically CAR-T cell therapy, growth factors, steroids, antineoplastic agents, folinic acid,

investigational drug, MESNA, rituximab) based on low usage within a UK setting, lack of unit cost data (e.g. CAR-T cell therapy) or relatively low cost (e.g. growth factors). Additional assumptions to align TKIs usage to UK clinical practice included imatinib being used to cost subsequent ponatinib treatments (since ponatinib is currently not reimbursed in the UK).

The ERG has identified several areas of uncertainties related to the drug costs and assumptions applied in the model. Firstly, the ERG considers that while it might be reasonable to include the additional cost of idarubicin within the modelled FLAG-IDA regimen, a case could equally be made for excluding this additional cost to ensure consistency between the efficacy outcomes and cost assumptions. Secondly, the inclusion of TKI costs for Ph+ patients without any adjustment in the efficacy outcomes appears overly optimistic towards the cost-effectiveness of inotuzumab. The limited evidence on the effectiveness of subsequent TKIs does not appear sufficient justification for assuming no impact on efficacy outcomes. Hence the ERG considers that the costs attributed to TKIs for Ph+ patients should not be included within the base-case.

Finally, the ERG acknowledge the issues raised by the company concerning the difficulties in controlling for the potential effect of subsequent induction therapies and note that a higher proportion of patients in the SoC arm receive these. The ERG considers that this uncertainty might be best considered within separate scenarios (i.e. exploring the impact of including/excluding these costs). However, the ERG is unclear why the proportion of patients receiving subsequent therapies was derived from the ITT and not the safety dataset. The ERG considers that this may create a positive bias towards inotuzumab. If any of the [redacted] of the SoC patients excluded from the safety population is included in these estimates of subsequent therapies, then the model will have attributed the costs but not the benefits. The ERG also notes that the base-case analysis uses list prices for these subsequent therapies which will not reflect any discounts to the NHS which may be available within existing PAS schemes. Hence, the ERG considers that it may be more appropriate to exclude the costs of subsequent therapies given these uncertainties while recognising that this assumption may be potentially conservative towards inotuzumab.

5.2.8.2 Administration, monitoring and concomitant medication costs

Inotuzumab and current SoC must be administered intravenously under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available. Table 17 summarises the administration costs applied to inotuzumab and the SoC regimens.

Table 17: Summary of administration costs

Treatment		Proportion of patients that receive treatment	Outpatient visits/ inpatient stays per cycle of treatment administered	Average administrations over treatment period	Outpatient/ inpatient cost	Total cost per patient for the average course of treatment	Source
Inotuzumab (n=164)		100%	3 administrations per cycle	2.8293	£304.30 per administration	**£2,582.80**	NHS ref costs
SoC (n=143)	FLAG-IDA	[redacted]	5 days inpatient	1.2903	£743.61 per inpatient day of administration	**£4,632.81** (weighted average based upon treatment use)	NHS ref costs
	CM	[redacted]	6 days inpatient	1.0215			
	HIDAC	[redacted]	5 days inpatient	1.0430			

CS, Table 64 – p229-230 (with the addition of the proportion of patients that receive treatment)

In response to clarification the company identified an error in the calculation of administration costs for CM and HIDAC, and supplied a corrected model in which the number of administrations is 1.0606 for CM and 1.2353 for HIDAC.

R/R ALL patients treated with standard chemotherapy in current UK practice are required to be admitted to hospital and treated on an inpatient basis. The inpatient stay assumed by the company for the SoC regimens was based on the duration of administration reported within the respective SPCs. However, the ERG considers that this is likely to significantly underestimate the length of stay for patients receiving conventional chemotherapy regimens. The ERG's clinical advisor indicated that patients are likely to remain hospitalised for significantly longer due to the subsequent recovery period which is typically 3-4 weeks in routine clinical practice and sometimes considerably longer for a second FLAG.

The ERG acknowledges that due to patient discontinuation and/or death, that the mean length of hospitalisation may be shorter. The ERG identified 2 potentially relevant and recent case studies which reported mean length of hospitalisation for Ph-negative R/R ALL patients between 16.8 days (France) and 26 days (Spain).[22, 23] Based on clinical advice and evidence from these case studies, the ERG considers that the company approach is likely to have significantly underestimated the administration costs for the SoC regimens.

The company noted that a potentially important benefit of inotuzumab is that it is administered in an outpatient setting allowing patients to return home after infusion. Hence, the company assumed that

the administration of inotuzumab would require 3 outpatient attendances during the 1st and subsequent cycles. The clinical advisor to the ERG did not consider that this assumption appropriately reflected how inotuzumab would be administered in a UK clinical setting. The ERG's clinical advisor stated that the majority of patients (and potentially even all patients) who receive inotuzumab would be admitted to hospital for that treatment for the first cycle and that the estimated length of stay would be approximately 4 weeks (i.e. from the start of treatment to discharge). The ERG's clinical advisor considered that if patients respond and go on to receive a second or subsequent cycle then that would be done as a day case.

As part of the clarification stage the ERG requested that the company discuss the generalisability of the assumptions made and to provide further data from INO-VATE 1022 on the number of patients treated on an inpatient basis. In their initial response the company stated that clinical expert opinion provided to them, suggested that: "*it is most likely that inotuzumab would be administered in an outpatient care setting, especially as familiarity with the treatment increases. If inpatient stay was required, this would likely be a factor of the disease itself rather that the treatment used*".

Response to ERG clarifications, Question A19 - p52

The ERG notes that there appears an important divergence between the clinical expert opinion received by the company and that received by the ERG. However, the company also provided further data from INO-VATE 1022 (see Table 18) which showed that approximately [redacted] of patients were hospitalised during Cycle 1 and that considerably fewer patients were hospitalised during subsequent cycles. The ERG considers that the current assumptions are likely to be optimistic in relation to the administration costs assumed for inotuzumab and that this represents an important area of uncertainty which has not been assessed within the company submission.

Table 18: Number and proportion of patients treated as an inpatient in INO-VATE 1022

[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Response to ERG clarifications, Table 1 - Question A19 p2-p4

For both treatment arms, disease monitoring was assumed to be captured in the outpatient/inpatient visit for administration and the adverse event costs. The total administration cost per treatment was applied as a lump sum in Cycle 0 for all patients.

5.2.8.3 HSCT costs

The costs associated with HSCT (initial procedure and follow up) were derived from the NHS Blood and transplant study (NHS Blood and Transplant, 2014) inflated to 2015/2016 prices. The cost of a HSCT comprised of the cost of transplant unit personnel and transplantation which included the cost of UK sourced cord blood donation.

The costs are summarised in Table 19 and are broken down into the costs of the procedure and associated follow up costs in the first 6 months, 6-12 months and 12-24 months after HSCT. The ERG considers that the source and assumptions employed by the company are appropriate.

Table 19: HSCT costs

Type of cost	Cost reported in NHS reference before inflation indices	Cost per cycle	Source
HSCT cost	£58,903	£60,891.72	NHS blood and transplant (2014) uplifted from 2012/2013 to 2015/2016 prices using PSSRU inflation indices. (297.0/287.3)(NHS Blood and Transplant 2014, Curtis 2016)
Post-HSCT in first 6 months	£28,390	£4,891.42	
Post-HSCT from 6–12 months	£19,502	£3,360.07	
Post-HSCT from 12–24 months	£14,073	£1,212.35	
Key: NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HSCT, haematopoietic stem cell transplant.			

CS, Table 66 - p52

5.2.8.4 Costs associated with adverse events

Costs associated with adverse events (AEs) were included in the model. Adverse events deemed relevant to the economic evaluation were those assessed Grade ≥3 and experienced by ≥5% of patients in either treatment arm. The rates of incidence were calculated from the frequency with which each AE occurred in the INO-VATE 1022 trial with the exception of graft-versus host disease (GvHD) which required data sourced from the literature (INO-VATE 1022 only captured deaths due to GvHD). It was assumed that the incidence of GvHD was not treatment specific.

The unit costs associated with each relevant adverse event were predominantly based on NHS Reference Costs, however the costs of treating VOD and GvHD were sourced from the external literature. Expert clinical opinion sought by the company indicated that severe VOD is treated with defibrotide in accordance with the guidelines set by the British Committee for Standards in Haematology. Given this advice, the unit cost applied to VOD events was informed by the submission for defibrotide to the SMC (2014). Using the methods of moments (Section 5.2.8.1) and the drug acquisition costs taken from the SMC submission, the total cost of defibrotide was estimated to be £77,240.11. The inpatient care necessary for treating VOD was taken from a published policy document by the NHS on the use of defibrotide in severe VOD following HSCT. The excess hospital stay due to severe VOD is reportedly 28.48 days. The cost per inpatient stay in the defibrotide SMC submission was £1,879, based on 85% of patients requiring intensive care and 15% requiring high dependency care, which was then inflated to £1,921 using the PSSRU inflation indices. Using the cost per hospital stay combined with the cost of defibrotide, the total cost for treatment of VOD was calculated to be £131,951.41. The SMC submission calculated that the total cost of defibrotide over a patient's lifetime was £92,836 (inflated to £94,913). In the company base case, the average of the two estimates was used.

The unit cost applied to GvHD was based on a single non-UK study which reported the costs that are associated with GvHD and multiple post-transplant episodes of bacterial, fungal, or viral infections. Choosing the most conservative estimate from the €20,000-€30,000 range (€30,000), the reported unit cost for GvHD was £26,888.92 after the initial figure was converted into sterling (2004) and inflated to 2015/2016 prices. Table 20 presents the unit cost per episode of managing the adverse events deemed relevant to the decision problem.

The total average cost of treating AEs while on treatment, was £576.41 in the inotuzumab arm and £1,239.23 in the SoC arm. A summary of the costs associated with AEs on treatment and post-HSCT are shown in Table 20. The ERG considers the sources and assumptions applied within the company model to be appropriate.

Table 20: Summary of total adverse event costs

Treatment	AE cost on treatment	AEs post-HSCT	Total
Inotuzumab	£2,622.50	£11,088.67	£13,711.17
SoC	£1,239.23	£689.45	£1,928.68
Key: AE, adverse event; HSCT, haematopoietic stem cell transplant; SoC, standard of care.			

CS, Table 69 – p236

5.2.8.5 End of Life Costs

The company applied a fixed cost (£11,616) to patients on entry to the death state based on cancer-specific end of life costs reported by the PSSRU (2016). These comprise the cost of hospital and social care reported for cancer-patients in the final year of life. It was also assumed that this cost also incorporates the cost of treating a progressed patient. Hence, no further costs were assumed within the progressed disease state.

The ERG requested further justification from the company regarding whether it is reasonable to apply costs derived over a 12 month period given the short life expectancy of many patients and whether it is appropriate to assign cancer costs to mortality events in the post-cure period. In their response, the company acknowledged that this was a simplifying assumption but provided further justification and a series of additional scenarios. The ERG acknowledges that the results indicate that the differences reported across these scenarios were minimal. The ERG thus considers the sources and assumptions reasonable and any uncertainties do not appear to have any material effect on the cost-effectiveness estimates.

5.2.9 Cost effectiveness results

5.2.9.1 Base case results

The company provided their base case cost-effectiveness results using the inputs and variables summarised in Appendix 10 of the CS. These results are presented in Table 21.

The base case results used a discount rate of 1.5% for costs and QALYs over a 60 year time horizon (CS, Section 5.2.5). The company found inotuzumab to be more costly (cost difference of [redacted]) but also more effective ([redacted]) compared with SoC. The resulting deterministic ICER is £40,013 per QALY gained.

Table 21: Base case cost-effectiveness results (1.5% discount rate)

	Costs	QALYs	LYs*	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£40,013
SoC	[redacted]	[redacted]	1.49	-	-		
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care. * estimates not discounted							

CS, Table 73 - p244

Table 22 provides a summary of the disaggregated results of the QALY gain which clearly shows that the majority of the QALY gain (approx. 95%) is conferred within the *HSCT & Post HSCT* state.

Table 22: Summary of discounted QALY gain by health state (1.5% discount)

Health state	QALY intervention Inotuzumab	QALY comparator SoC	Increment	Absolute increment	% absolute increment
No CR/CRi	[redacted]	[redacted]	[redacted]	[redacted]	2.65%
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	2.36%
HSCT& Post HSCT	[redacted]	[redacted]	[redacted]	[redacted]	94.99%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; QALY, quality-adjusted life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

CS, Table 77 – p246

Results were also reported using a 3.5% discount rate in line with the conventional NICE reference case requirement (CS, Appendix 11). These results are presented in Table 23 and the higher discount rate increases the base-case ICER to £55,869 per QALY.

Table 23: Base case cost-effectiveness results (3.5% discount rate)

	Costs	QALYs	LYs*	Incremental			ICER
				Costs	QALYs	LYs	
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£55,869
SoC	[redacted]	[redacted]	1.49				

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care, *estimates not discounted

CS Appendix, Table 126 – p171

5.2.9.2 Sensitivity analyses

Deterministic sensitivity analysis

The company presented a series of one-way deterministic sensitivity analyses to assess the impact of varying key model input parameters on the ICER. Figure 11 shows a tornado diagram summarising the 10 most influential parameters reported by the company.

Figure 11: Tornado diagram

CS, Figure 56 – p252

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions based on 5,000 simulations. The ICER results from the PSA were higher than from those of the deterministic analysis, as shown in Table 24 and Table 25.

The mean probabilistic ICER was £48,459 per QALY for a discount rate of 1.5% (Table 24) and £67,575 for a discount rate of 3.5% (Table 25). The cost-effectiveness plane and acceptability curves were presented in the CS. With a 1.5% discount rate, the probability that inotuzumab is cost-effective at a threshold value of £50,000 per additional QALY is 0.45 compared with standard therapy. This probability falls to 0.27 at the conventional 3.5% discount rate.

Table 24: Results of the company's probabilistic sensitivity analysis discounted at 1.5%

	Incremental			ICER (inotuzumab vs SoC)
	Costs	QALYs	LYs	
Costs and benefits discounted at **1.5%**	[redacted]	[redacted]	4.69	£48,459
Key: ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.				

CS, Table 81 – p248

Table 25: Results of the company's probabilistic sensitivity analysis discounted at 3.5%

	Incremental			ICER (inotuzumab vs SoC)
	Costs	**QALYs**	**LYs**	
Costs and benefits discounted at **3.5%**	[redacted]	[redacted]	4.70	£67,575
Key: ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.				

CS Appendix, Table 130 – p174

The company provides several caveats for the higher probabilistic ICER. First, the uncertainty seen from the post HSCT OS was subject to small patient numbers and while the survival curves attain a clinically justified plateau, the uncertainty uncovered in the PSA comes from investigating parameters that vary this plateau. The company concluded that such variation in the plateau should be treated as artificial uncertainty within the model. Secondly, the change in mortality rate past the cure point may not be reflected in the PSA where the variance of parameters was, to a degree, related to the shape of the pre-cure OS curve which captures higher rates of mortality. Thirdly, the company reiterates the point that making a decision about the cost-effectiveness of inotuzumab based on the cost-effectiveness of HSCT, which is already used in the UK, could be considered outside the remit of this appraisal.

The ERG considers that the probabilistic ICERs represent the most appropriate estimates for the purposes of decision making. The higher probabilistic ICERs indicate that there are important non-linearities in the model that should be accounted for in the mean ICER estimates.

The submission also included an extensive series of scenario analyses to check the robustness of the model results to uncertainty relating to survival data, parameters, and structural assumptions. The large majority of the company's scenario analyses showed that the cost-effectiveness of inotuzumab compared with standard therapy appeared relatively insensitive to changes in the structural assumptions, with the ICERs at a 1.5% discount rate varying from approximately £30,576 to £44,464 and £41,610 to £54,723 per QALY gained in deterministic and probabilistic key scenarios, respectively.

5.2.10 Model validation and face validity check

The company states that the cost-effectiveness model was validated with respect to its structure and predictive validity. The model structure and assumptions were reviewed by multiple UK clinical experts and deemed applicable to the decision problem. The technical accuracy of the calculations of

costs and QALYs within the model was verified by the developers of the model on behalf of the company. In addition, several (unspecified) quality control measures were undertaken to validate the models findings and an independent modeller critiqued the structure, parameter inputs, and core assumptions.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. However, the ERG identified a number of key uncertainties. The main concerns expressed by the ERG relate to the following issues:

1. *The lack of a structural link between remission outcomes (CR/CRi) and HSCT*
   The ERG considers that the decision to model HSCT outcomes independently of CR/CRi outcomes significantly limits the model, particularly in terms of subsequent subgroup analyses. CR/CRi is usually a pre-requisite for HSCT in UK clinical practice. Furthermore, incorporating a structural link between CR/CRi and HSCT would have provided a more appropriate basis to explore the impact of population characteristics (e.g. age, salvage status, prior SCT, duration of remission, Philadelphia chromosome and region) and their potential impact on survival and QALYs.
2. *The complexity of the parametric modelling approach*
   The ERG considers that the parametric modelling introduces potentially unnecessary complexity. Given the completeness/near-completeness of the Kaplan-Meier data for two of the states (*CR/CRi & no HSCT* and *No CR/CRi & No HSCT*), the additional advantages conferred by parametric modelling approaches appear to be largely confined to the *HSCT & Post HSCT* state. The ERG considers that an alternative option would be to make greater use of the Kaplan-Meier data.
3. *The assumption of additional mortality benefit for inotuzumab within the 'HSCT & post HSCT' state*
   The ERG does not consider the assumptions employed in the parametric modelling approach applied in the company base-case for the *HSCT & Post HSCT* state are robustly supported by the existing data. The ERG also has concerns regarding the clinical plausibility and external validity of the extrapolated results for this state.
4. *The choice of the cure time point*
   The ERG is concerned that the justification for the 3 year point assumed in the base-case appears largely determined on the basis of the clinical plausibility of the survival projections based on the parametric modelling approach as opposed to reflecting the most clinically

appropriate point. The ERG considers that a cut point of 3 years could be potentially optimistic and may more appropriately reflect a lower bound.

5. *The cure assumption*
   The ERG considers that there remains significant uncertainty surrounding the longer-term survival of post HSCT patients. Existing epidemiological evidence suggests that patients remain at higher risk of mortality for up to 30 years after HSCT. Although the risks decline with time, the mortality risks of patients surviving at least 5 years after HSCT without relapse remains considerably higher than the general population (between 4-9 times higher, irrespective of age).
6. *The inclusion of the costs of subsequent induction therapies*
   The ERG considers that it may be more appropriate to exclude the costs of subsequent therapies.
7. *The administration costs of current SoC regimens and inotuzumab*
   Based on clinical advice and case studies, the ERG considers that the company model is likely to significantly underestimate the administration costs for the SoC regimens. The ERG also considers that the assumptions that inotuzumab will be administered in an outpatient setting for all treatment cycles does not reflect clinical advice received regarding how the treatment would be administered in a UK clinical setting. Data from INO-VATE 1022 also indicate that a significant proportion of patients received inotuzumab in an inpatient setting.
8. *The need to age-adjust utility estimates applied to the 'HSCT & Post HSCT' state*
   When utility values are considered over the 60-year lifetime horizon then it is evident that the utility values assigned to the post-HSCT state may eventually exceed general population utility estimates, which naturally decline with age. The ERG thus considers that utilities in the post-HSCT state should be further adjusted for age as reported within a separate scenario by the company.

Given the importance of a number of these issues, additional analyses that were either requested by the ERG from the company or independently undertaken by the ERG are presented in Section 6, which consider the potential impact of the remaining uncertainties on the cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section focuses on the additional analyses used to explore the key areas of uncertainty and concern highlighted in Section 5. These analyses are constrained to the population and comparators provided within the company submission. A structural link between remission outcomes and HSCT could be informed by analysis of patient level data that estimates the likelihood of receiving HSCT as a function of CR/CRi and other patient characteristics. However, these data were not available to the ERG.

The main changes made by the ERG to the economic model are aimed at addressing the concern about the suitability and complexity of the parametric modelling. Additional analyses are used to explore the impact of alternative assumptions about whether intozumab offers additional survival benefits post HCST and whether HSCT can be considered curative.

The ERG also adjust the administration costs used in the model to reflect the potential for patients to reside in hospital for a recovery period following receipt of standard chemotherapy or inotuzumab. The ERG model is then used to explore the impact of assuming costs more in line with current NHS practice, although it is not possible to provide any corresponding adjustments to efficacy.

6.2 ERG corrections and adjustments to the company's base case model

The company submission acknowledged many of the uncertainties discussed in Section 5, and the company model incorporated a range of scenario analyses that allowed the impact of alternative assumptions to be explored. In response to points for clarification, the company added additional scenario analyses and functionality to the model around post HSCT survival and the costs of subsequent induction therapies. The following sections provide further information about the company changes in response to clarification and describe additional adjustments made by the ERG to:

- the model structure to allow for the use of non-parametric Kaplan-Meier data (Section 6.2.1);
- determine a value for an increased standardised mortality rate post cure (Section 6.2.2), and;
- recalculate the administration costs (Section 6.2.5).

6.2.1 Treatment effectiveness and extrapolation

As noted in Section 5.2.6, the ERG has concerns about the extent and complexity of the parametric survival analysis, and does not consider the parametric models fit to the *HSCT & Post-HSCT* sub

population to be a suitable basis for extrapolation. In response to clarification, the company provided pooled Kaplan-Meier data and a pooled parametric survival analysis for the *HSCT & post HSCT* sub population. Table 26 shows the results from this additional scenario for a deterministic analysis using a 1.5% discount rate. The company also supplied these results for discount rates of 3.5% and from the probabilistic analysis (see CS response to clarification B4). The ERG notes that the discrepancy between the deterministic and probabilistic ICER is much less for this scenario analysis (~£2,000) compared to the company base case.

Table 26: Scenario analysis using pooled post HSCT in both treatment arms (safety) – deterministic (1.5% discount rate)

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	Lys	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£85,512
SoC	£64,616	1.20	2.93				
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care							

Response to ERG clarification B4, Table 6 - p73

The benefits of treatment with inotuzumab characterised in the company base case can be condensed into three main effects:

(i) increasing the rate of CR/CRi

(ii) increasing the rate of HSCT

(iii) improving survival post HSCT

To illustrate the amount by which each of these affect the overall QALY gain for inotuzumab compared to standard of care, the ERG re-ran the company model introducing each element in turn. To estimate the benefit of inotuzumab in terms of only increasing the rate of CR/CRi, the proportion of patients proceeding to HSCT was set to zero, with these patients redistributed between the *No CR/CRi & no HSCT* and *CR/CRi & no HSCT* health states in accordance with their CR/CRi results. To estimate the benefit of inotuzumab in terms of increasing the rate of CR/CRi and increasing the rate of HSCT, the model scenario using pooled post-HSCT survival (supplied in response to clarification) was used. Table 27 illustrates the results, showing how each additional element of treatment effect affects the overall QALY gain in the company base case.

Table 27: Incremental QALY benefit of inotuzumab for different elements of treatment effect

	Discount rate 1.5%				Discount rate 3.5%			
Assumed treatment benefit	Inc. cost	Inc. QALY	ICER	added QALY benefit*	Inc. cost	Inc. QALY	ICER	added QALY benefit*
Rate of CR/CRi only	[redacted]	[redacted]	£546,635	[redacted]	[redacted]	[redacted]	£545,297	[redacted]
Rate of CR/CRi and rate of HSCT	[redacted]	[redacted]	£85,512	[redacted]	[redacted]	[redacted]	£115,360	[redacted]
Rate of CR/CRi, rate of HSCT and survival post HSCT (company base case)	[redacted]	[redacted]	£40,013	[redacted]	[redacted]	[redacted]	£55,869	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Inc. cost = incremental cost compared to standard of care; Inc. QALY = incremental QALY compared to standard of care; * shows difference in incremental QALY gain compared to preceding row

The benefit of inotuzumab on increasing the rate of CR/CRi alone is estimated to provide [redacted] incremental QALYs, compared to the [redacted] incremental QALYs estimated for inotuzumab versus standard of care in the company base case. Adding in the benefit of inotuzumab in increasing the rate of HSCT increases the incremental gain by a further [redacted] QALYs. Finally, assuming that inotuzumab also improves post HSCT survival adds a further [redacted] QALYs.

The company also presented an alternative scenario where the treatment benefit of inotuzumab is in terms of: (i) increasing the rate of CR/CRi; (ii) increasing the rate of HSCT, and; (iii) increasing the rate of MRD-negativity, where MRD status is assumed to determine post-HSCT survival (CS Table 83 and Appendix 7). The results of the company model were re-calculated by the ERG using this additional scenario, as shown in Table 28.

Table 28: Scenario analysis using pooled post-HSCT survival with MRD covariate – deterministic (1.5% discount rate)

	Costs	QALYs	Incremental		ICER
			Costs	QALYs	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£56,819
SoC	£64,383	0.92			

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care

In this scenario inotuzumab increases the rate of MRD-negativity in patients in the *HSCT & post HSCT* health state from [redacted] with standard of care to [redacted]. Using a discount rate of 1.5%, the impact of inotuzumab on increasing the rate of MRD-negativity is estimated to add an additional [redacted] QALYs on top of the incremental QALY gains estimated from increasing the rate of CR/CRi and rate

of HSCT, producing an overall QALY gain of [redacted] and an ICER of £56,819. The corresponding results using a discount rate of 3.5% are an additional [redacted] QALYs and an overall [redacted] QALY gain, with an ICER of £77,783.

In response to clarification the company provided additional Kaplan-Meier data for each sub population for both the ITT and the safety population. The ERG adapted the company model in order to predict survival directly from the Kapan-Meier data for each sub-population. While the Kaplan-Meier data is complete for the *No CR/CRi & no HSCT* health state, within the *CR/CRi & no HSCT* sub population the final point on the Kaplan-Meier OS curve is [redacted] on the intotuzumab arm and [redacted] on the standard of care arm (which in terms of the overall population represents [redacted] and [redacted] respectively). Using only the Kaplan-Meier data, the survival curves in the *CR/CRi & no HSCT* health state are truncated at the last observed follow-up, with the assumption that all patients remaining alive immediately die. To avoid truncating the survival curves for the *HSCT & Post HSCT* sub population, the 'cure' point was set to 2.75 years from the point of HSCT, i.e. the extent of the Kaplan-Meier data. The last observed point in the Kaplan-Meier data for the *HSCT & Post HSCT* sub population is [redacted] survival on the inotuzumab arm and [redacted] on the standard of care arm (which in terms of the overall population represents [redacted] and [redacted] respectively). In the *HSCT & Post HSCT* sub population approximately [redacted] of patients on the inotuzumab arm and [redacted] of patients on the standard of care arm remain progression free at the end of the Kaplan-Meier PFS data, which extends to [redacted] years and [redacted] years respectively. For these patients we assumed no further progression events.

This simple non-parametric approach makes the most use of the observed trial data, but does force the choice of 'cure' point and will be sensitive to additional events that would alter the tail of the Kaplan-Meier curve. In principle it would be possible to build a model that used the Kaplan-Meier data for the initial period and then switched to a parametric extrapolation, either when the effective sample size is considered to become too small or the Kapen-Meier data end.[24] The most suitable parametric survival models for this type of hybrid approach do not necessarily match those provided in the company base case, as the models may estimate to better fit the 'tail' of the Kaplan-Meier data. The hybrid approach could be considered unnecessary given the company selected 'cure' point of 3 years. For OS there is near completeness of the Kaplan-Meier data in the *CR/CRi & no HSCT* and *No CR/CRi & no HSCT* health states, such that any parametric extrapolation would largely be confined to the *HSCT & Post HSCT* state over a period of approximately 3 months. Using a 'cure' point of 3 years, additional events that may be observed beyond 3 years could significantly alter the tail of the Kaplan-Meier OS curve but would not influence the model results. The Kaplan-Meier PFS data are

less complete for the *HSCT & Post HSCT* state, but the parametric models employed by the company have begun to plateau at [redacted] years and predict no further progression events beyond [redacted] years. The simple non-parametric approach combined with an assumption of no further progression at the end of the Kaplan-Meier data in effect forces an earlier plateau compared to the fully parametric approach. The ERG considered that the recreation of individual patient data for further parametric survival analysis and the series of further assumptions that would be required to undertake the hybrid approach were neither achievable within the time available, nor likely to be useful.

The simple non-parametric approach to survival analysis can be applied with the separate Kaplan-Meier data for each treatment arm for the *HSCT & Post HSCT* sub population. Alternatively, it can be combined with the pooled Kaplan-Meier data for the *HSCT & Post HSCT* sub population. [redacted] As discussed in Section 5.2.6, both the ERG and company note that the survival differences post HSCT are based on small sample sizes and evaluated post-randomisation, and so should be interpreted with caution. Consequently, the ERG non-parametric base case uses the pooled survival data for the *HSCT & Post HSCT* health state. Survival at 2.75 years in the pooled Kaplan-Meier OS data is [redacted] (see Response to ERG clarification B3 Figure 22 - p73), which in terms of the overall population would represent [redacted] of patients in the inotuzumab arm and [redacted] of patients in the standard of care arm.

To distinguish the impact of converting the company model to use the Kaplan-Meier data directly from the impact of assuming pooled post HSCT survival, the ERG also present a non-parametric version of the company base case by utilising the separate Kaplan-Meier data post HSCT by treatment arm.

The ERG acknowledges that a hybrid or fully parametric approach is required for exploring the impact of alternative 'cure' points, and may also mitigate concerns about uncertainty in the tail of the Kaplan-Meier data when few patients remain at risk.[25] As such, in addition to the simple non-parametric approach, the ERG presents amendments to the fully parametric scenario provided by the company in which survival differences post HSCT are determined by MRD status. The ERG parametric base case is used to explore the impact of alternative time points after which HSCT may be considered 'curative'.

6.2.2 Mortality beyond the trial follow up

In response to clarification, the company adapted the model to allow for an increased standardised mortality rate compared to the general population. As noted in Section 5.2.6.1, the ERG considers

that post HSCT patients would continue to experience an elevated mortality compared to the general population.

The extent of the elevated risk is uncertain, but several studies have compared the long-term survival of hematopoietic stem cell transplantation against the general population[15-17] and against cancer survivors who did not receive HSCT.[26] These studies differ in the sample size, duration of follow up, and the inclusion criteria regarding survival post HSCT. Wingard et al. included patients that received HSCT between 1980-2003 and has one of the largest cohorts, with a median follow-up of 9 years; they calculate that the relative risk of mortality for ALL 2-year survivors of HSCT remains greater than 10 for up to 15 years post-transplant. The study by Martin et al. included patients that received HSCT between 1970-2002 and has longer follow-up (median 13.1 years); it reports that in 5-year survivors of HSCT mortality remains four to nine-fold higher than the general population for up to 25 years post-transplant. The more recent study by Chow et al. included patients that received HSCT between 1992-2009 and reports increased morbidity and mortality for HSCT survivors both compared to the general population and compared to non-HSCT cancer survivors.

The ERG preferred base case is to use a fourfold higher mortality rate, in line with the lower bound of the range estimated in Martin et al. (2010).[16] The use of the lower bound is conservative, but could mitigate concerns about the historic nature of the cohort required for this type of long-term outcome analysis.

6.2.3 Health-related quality of life

The ERG preferred base case makes use of the pooled on treatment utility values, as per the company scenario analysis. As noted in Section 5.2.7 the ERG believes it is appropriate to apply the age adjusted utilities.

The ERG base case retains the assumption from the company base case that patients who progress post HSCT experience a lower health related quality of life compared to those that do not progress, but notes that as the majority of patients are estimated to progress in the model, this may be at odds with assuming a long life expectancy for those 'cured' post HSCT. As such, the ERG also presents the scenario analysis using Kurosawa utilities for all patients post HSCT, i.e. in which progression post HSCT is assumed not to influence patient quality of life.

6.2.4 Drug acquisition costs

As noted in Section 5.2.8.1, the ERG believes that including the costs of therapies when the benefits are excluded is inappropriate. Therefore the ERG preferred base case matches the costs to the actual

therapy received in INO-VATE 1022. This assumes that patients are split between FLAG, CM and HIDAC as observed in INO-VATE 1022 and that the cost of TKIs is not included for Ph+ patients. In the case of subsequent induction therapies it is unclear whether the benefits are included or not due to the use of the safety population. Given the uncertainty in the price of these therapies the ERG preferred base case makes use of the company scenario where the costs of blinatumomab and inotuzumab as second line induction therapies are replaced with the cost of chemotherapy. As this may be conservative towards inotuzumab, they are included in a sensitivity analysis.

The ERG believes that it may be useful to look at the estimated cost of standard of care if all patients are assumed to receive FLAG-IDA in line with current NHS practice instead of a mix of FLAG, CM, and HIDAC. This is provided as a sensitivity analysis to the ERG base case, while noting it may be conservative towards standard of care given that efficacy is not adjusted.

6.2.5 Resource use and costs

When responding to the points for clarification, the company noted that they had found an error in the economic model in calculating the administration costs for CM and HIDAC. The model provided in response to clarification incorporated a "fix" for this, which is utilised in the ERG base case.

As noted in Section 5.2.8.2 the ERG has concerns that the company base case significantly underestimates the amount of inpatient stay required for administration of inotuzumab and standard of care. The ERG preferred base case assumes that the proportion of patients who receive inotuzumab administered on an inpatient basis matches that observed in the INO-VATE 1022 trial (CS response to clarifications, Table 1 - Question A19 p2-p4). These results indicate that out of an average 2.83 administrations, [redacted] were received on an inpatient basis and [redacted] on an outpatient basis. While some patients in the INO-VATE 1022 trial appear to have received standard of care chemotherapy on an outpatient basis, the ERG preferred base case maintains the assumption that all standard of care chemotherapy is provided on an inpatient basis.

The inpatient stay assumed by the company was based on the duration of administration reported within the SPCs for the standard of care therapies, and does not reflect any additional time spent in hospital for recovery. The company base case calculates the cost per inpatient day of administration based on the NHS Reference cost for an elective inpatient "Acute Lymphoblastic Leukamemia with CC score 0-1", which is associated with a cost of £3,651 for an average length of stay of 4.91 days. The ERG notes that there are costs available for higher complication and comorbidity scores: "Acute Lymphoblastic Leukaemia with CC score 2-4" costing £5,060 for an average length of stay 7.26 and "Acute Lymphoblastic Leukaemia with CC score 5+" costing £12,685 for an average length of stay

19.02.([27]) By taking a weighted average across all CC score categories, the ERG calculated a weighted average administration cost of £6,543 and a weighted average length of stay of 9.5 days, giving a cost per bed day of £691. In the ERGs preferred base case the length of stay is kept consistent with the source of the cost per bed day by basing both on the NHS reference cost data.

These two changes increase the total cost per patient for the average course of treatment from £2,583 to £9,277 for inotuzumab and from £4,633 (uncorrected company base case) to £8,053 for standard of care. The administration cost of inotuzumab exceeds that of standard care because patients in the standard of care arm on average had only 1.23 administrations (split across 1.29 for FLAG, 1.06 for CM and 1.24 for HIDAC), whereas patients receiving inotuzumab had [redacted] inpatient admissions and an additional [redacted] outpatient admissions (with each outpatient admission requiring 3 visits at a cost of £304 per visit). The ERG also calculated the administration costs based on the length of inpatient stay increased to 26 days to characterise 5 days of administration followed by a 3 week recovery period. This reflects clinical advice to the ERG that administration of FLAG-IDA and inotuzumab are associated with recovery periods in hospital of about 3-4 weeks. With a minimum length of stay of 26 days, the cost per patient for the average course of treatment increases to £22,846 for inotuzumab and £22,098 for standard of care.

6.2.6 Uncertainty

The probabilistic sensitivity analysis applied to the company's base case analysis included distributions assigned to patient characteristics. This is considered inappropriate for probabilistic sensitivity analysis as it conflates variability in patient characteristics with uncertainty in the prognostic value of patient characteristics. The ERG re-ran the company's probabilistic model on four occasions with and without assuming a fixed set of cohort characteristics in order to understand the impact of parameter uncertainty and variability. This resulted in little change to the company probabilistic ICER as shown in Table 29.

Table 29: Probabilistic ICERs with and without fixed patient characteristics

	Probabilistic ICER: Company base case	Probabilistic ICER: Fixed patient characteristics
Run 1	£48,304.30	£50,159.10
Run 2	£48,304.30	£49,828.94
Run 3	£47,889.20	£50,578.81
Run 4	£48,182.91	£49,708.11

Within the time available it was not possible to incorporate functionality in the model to undertake a probabilistic sensitivity analysis that incorporates uncertainty in the Kaplan-Meier data across the

three sub-populations. Therefore the results of the ERG base case are reported for deterministic analysis. However, the ERG notes that the probabilistic ICER is the most relevant to inform cost effectiveness, and that this would probably be larger than the deterministic results.

6.3 Additional ERG analyses

Table 30 summarises the relevant scenarios provided by the company and the additional amendments to the company base case undertaken by the ERG.

Table 30: Relevant scenarios provided by company and undertaken by ERG

Key	
Scenario	**Description**
1. Fix from CS response	Minor model correction: proportion of patients receiving cycle 2 treatments CM and HIDAC now linked to CM/HIDAC as opposed to FLAG.
Relevant scenarios conducted by the company	
2. Parametric survival functions: pooled survival with MRD	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.
3. Age adjusted utilities	Applies age adjusted utilities into the model.
4. Chemotherapy costs in line with INO-VATE	Remove the costs of TKI imatinib for Ph+, assumes SoC patients split between FLAG, CM and HIDAC and excludes the costs of idarubicin.
5. Pooled on treatment utilities	Utilities are not treatment specific.
Changes provided in response to ERG clarifications	
6. Subsequent therapy costs in line with chemotherapy	Costs for patients receiving blinatumomab and inotuzumab are replaced with the cost of chemotherapy.
Changes conducted by ERG	
7a. Non-parametric survival data with pooled post-HSCT survival	Uses Kaplan-Meier data directly with the 'cure' point set at 2.75 years post-HSCT, and with pooled survival post-HSCT. Assumes no further progression beyond Kaplan-Meier PFS data.
7b. Non-parametric survival data with separate survival curves post HSCT	Uses Kaplan-Meier data directly with 'cure' point set at 2.75 years post-HSCT and separate survival curves post HSCT. Assumes no further progression beyond Kaplan-Meier PFS data.
8. Fourfold increase in risk of mortality post-cure	Applies a four-fold risk ratio to the general population mortality hazard for individuals post 'cure'.
9. Weighted average NHS administration costs and length of inpatient stay. Administration of inotuzumab as per INO-VATE 1022.	Alternate administration costs based on a weighted average NHS reference cost (see Section 6.2.5). The patient setting for inotuzumab administration is aligned with INO-VATE 1022 and includes a proportion delivered as inpatient.

The ERG non-parametric base case is composed of scenario **1 + 3 + 4 + 5 + 6 + 7a + 8 + 9**. An alternative parametric base case is provided composed of scenario **1 + 2 + 3 + 4 + 5 + 6 + 8 + 9** in order to facilitate further sensitivity analysis and to show the impact of assuming that inotuzumab improves post HSCT survival through increasing the rate of MRD negativity. Both ERG base cases

employ a discount rate of 3.5% for costs and for health outcomes to reflect the fact that R/R B cell ALL patients who survive post HSCT continue to experience higher morbidity and mortality compared to the general population. However, the main results are provided for a discount rate of 1.5% for both costs and health outcomes.

The ERG also conducted a series of sensitivity analyses. In the ERG non-parametric base case these include:

- SA1: All standard of care costed as FLAG-IDA
- SA2: Including list price of blinatumomab and inotuzumab as subsequent induction therapies
- SA3: Assuming 26 days inpatient stay for administration
- SA4: Assuming no additional mortality risk compared to the general population post cure
- SA5: Using the Kurosawa utility values for all patients in the *HSCT & Post HSCT* state (i.e. assuming no impact of progression on health related quality of life post HSCT)
- SA6: Using separate survival curves for inotuzumab and standard of care post HSCT

The ERG also presents the impact on the results from using combinations of the above sensitivity analyses. In the ERG parametric base case further sensitivity analysis is used to explore alternative time points after which HSCT may be considered 'curative'.

6.3.1 Results of the ERG corrections and adjustments

Figure 12 compares the observed Kaplan-Meier data against the model predictions from the company base case and the ERG non-parametric base case. While the ERG base case makes use of the Kaplan-Meier data directly, it uses the pooled Kaplan-Meier data across treatment arms for individuals who received HSCT. Hence it does not overlap precisely with the separate Kaplan-Meier OS data for each treatment. It is apparent from Figure 12 that the main difference between the ERG base case and the company base case is in the proportion on standard of care that remain alive for the long-term extrapolation.

Figure 12: Observed Kaplan-Meier overal survival compared to model predictions

OS: Overall survival; K-M: Kaplan-Meier; SoC: Standard of Care

When all three approaches are compared in terms of the model predicted overall survival for the whole population at 3 years:

- the company base case predicts [redacted] for inotuzumab and [redacted] for standard of care;
- the ERG non-parametric base case predicts [redacted] for inotuzumab and [redacted] for standard of care;
- the ERG parametric base case predicts [redacted] for inotuzumab and [redacted] for standard of care.

Table 31 shows the effect of individual changes on the company base case ICER, and how these are combined to produce the ERG preferred base case estimates using a discount rate of 3.5%. The discount rate itself is influential, as the company base case ICER increases from £40,013 to £55,869 when a rate of 3.5% is used for costs and health outcomes. The same set of individual changes are shown using a discount rate of 1.5% in Appendix 10.2.

Table 31: Results of relevant scenarios and additional calculations for ERG base cases

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change from company ICER

Company base case results - deterministic (3.5% discount rate)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£55,869	n/a
Standard of Care	£65,899	0.49				
1. Fix from CS response						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£55,779	-£90
Standard of Care	£66,079	0.49				
2. Parametric survival functions: pooled survival with MRD ('cure' point 3 years post HSCT)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£77,783	+£21,914
Standard of Care	£63,818	0.74				
3. Age adjusted utilities						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£60,260	+£4,391
Standard of Care	£65,899	0.48				
4. Chemotherapy costs in line with INO-VATE						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£57,287	+£1,418
Standard of Care	£63,411	0.49				
5. Pooled on treatment utilities						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£55,992	+£123
Standard of Care	£65,899	0.49				
6. Subsequent therapy costs in line with chemotherapy						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£61,594	+£5,725
Standard of Care	£52,365	0.49				
7a. Non-parametric survival data with pooled post-HSCT survival						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£83,060	+£27,191
Standard of Care	£63,933	1.18				
7b. Non-parametric survival data with separate survival curves post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£56,483	+£614
Standard of Care	£65,706	0.90				
8. Fourfold increase in risk of mortality compared to general population post-cure						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£68,381	+£12,512
Standard of Care	£65,930	0.46				

9. Weighted average NHS administration costs and length of inpatient stay						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£57,804	+£3,165
Standard of Care	£70,457	0.49				
ERG non-parametric base case: 1 + 3 + 4 + 5 + 6 + 7c + 8 + 9						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£122,174	+£66,305
Standard of Care	£53,332	0.98				
ERG parametric base case 1 + 2 + 3 + 4 + 5 + 6 + 8 + 9						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£114,078	+£58,299
Standard of Care	£53,165	0.65				

Scenario 7b is not included in the ERG base case, but is presented to demonstrate that the switch from the company base case to a non-parametric approach has little impact on the ICER, although it does increase estimated survival in both arms. The company parametric base case extrapolates a survival rate difference of [redacted] post HSCT when compared to patients in whom HSCT is preceded by standard of care. The use of separate Kaplan-Meier data with a cure point of 2.75 years in the non-parametric approach increases this extrapolated survival rate difference to [redacted]

In contrast, scenario 7a shows that removing the assumption that inotuzumab increases post HSCT survival increases the company base case ICER to £83,060 per QALY gained compared to standard of care (discount rate 3.5%). If, as per scenario 2, the treatment effect of inotuzumab on post HSCT survival is assumed via MRD status, this increases the ICER by a lesser amount to £77,800 per QALY gain compared to standard of care.

The ERG base case predicts similar total costs for inotuzumab as for the company base case, but lower costs for standard of care, largely due to the removal of additional costs for therapies not received in INO-VATE 1022 and the exclusion of costs for blinatumomab and inotouzumab received as subsequent induction therapies. Compared to the company base case, the ERG base predicts slightly lower QALYs for inotuzumab due to the inclusion of age-adjustment to utilities and an increased mortality risk compared to the general population post HSCT. The ERG base case predicts higher QALYs for standard of care compared to the company base case by removing the assumption of differential survival benefits post HSCT. The ERG non-parametric base case ICER is £122,174 per QALY gained with inotuzumab compared to standard of care. If a discount rate of 1.5% is applied to costs and health outcomes, the ERG non-parameric base case ICER is £97,988. The ERG parametric base case ICER is £114,078 for a discount rate of 3.5% and £90,982 for a discount rate of 1.5%.

Table 32 shows the summary of the discounted QALY gain by health state for the ERG non-parametric base case. The QALY gains in the *No CR/CRi & no HSCT* and *CR/CRi & no HSCT* health states are almost identical to those for the company base case, and the majority of the health gains (87% of the summed absolute increments) are in the *HSCT & Post HSCT* health state. A similar pattern is observed for the ERG parametric base case, in which the *HSCT & Post HSCT* QALY gains are estimated to be 1.39 for inotuzumab and 0.45 for standard of care, giving an increment of 0.94 which represents 89% of the summed absolute increments.

Table 32: Discounted QALY gain by health state in ERG non-parametric base case (3.5% discount)

Health state	QALY intervention InO	QALY comparator SoC	Increment	Absolute increment	% absolute increment
No CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	6.24%
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]	[redacted]	7.22%
HSCT& Post HSCT	[redacted]	[redacted]	[redacted]	[redacted]	86.54%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; InO, inotuzumab ozogamicin; QALY, quality-adjusted life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Table 33 shows the total cost by component for the ERG non-parametric base case. The majority of the incremental cost with inotuzumab is due to the cost of the drug itself and associated adverse events, in particular the increased rate of VOD. The remainder is largely accounted for by increased costs associated with HSCT, as more patients receiving inotuzumab receive HSCT compared to standard of care.

Table 33: Components of total discounted costs in ERG non-parametric base case

Cost component	Inotuzumab	Standard of care	Absolute increment
Treatment	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
Associated with HSCT	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]

End of life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

6.3.2 Sensitivity analyses for ERG base case

Table 34 summarises the sensitivity analysis for the ERG non-parametric base case. The results of the same sensitivity analyses but using a lower discount rate of 1.5% can be found in Appendix 10.2. Assuming all patients in the standard of care arm receive the costs of FLAG-IDA (SA1) has little impact on the results. Including the costs of blinatumomab and inotuzumab as subsequent induction therapies (SA2) increases the estimated costs for both arms, but by a larger amount for standard of care, and hence the estimated ICER falls by approximately £10,000. Assuming administration of standard of care or inotuzumab in an inpatient setting results in a stay of 26 days (SA3) increases the costs for both arms, again by a larger amount for standard of care. The impact of all three of these cost sensitivity analyses combined (SA1 + SA2 + SA3) is to reduce the ERG base case ICER by about £8,000.

Assuming that patients who are 'cured' post HSCT experience the same mortality risk as the general population (SA4) increases the estimated QALYs for both treatments, but more so for inotuzumab, reducing the ICER to £102,625. Assuming that progression post HSCT has no impact on health related quality of life (SA5) similarly increases the estimated QALYs, reduces the ICER. These together (SA4 + SA5) characterise a situation in which HSCT is considered curative, and produce an ICER of £83,286. Using the separate Kaplan-Meier curves post HSCT and extrapolating the survival rate difference from the tail of the Kaplan-Meier data in the *HSCT & post HSCT* population (SA6) increases the QALYs estimated for inotuzumab and reduces the QALYs estimated for standard of care, which leads to a large drop in the ICER to £84,065. If this analysis is combined with an assumption that those surviving beyond the cure point experience the same mortality risk as the general population (SA4 + SA6), the ERG base case ICER is reduced to £70,521. If it is further assumed that those surviving do so with utility scores based on Kurosawa (i.e. that do not reflect the impact of progression on health related quality of life), the ERG base case ICER falls to £52,940 per QALY gained (SA4 + SA5 + SA6). It is only when all of these sensitivity analyses are combined that the ICER falls below £50,000 per QALY.

Table 34: Sensitivity analysis for ERG non-parametric base case

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change from base case ICER

ERG non-parametric base case results - deterministic (3.5% discount rate)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£122,174	n/a
Standard of Care	£53,332	0.98				
SA1. All standard of care costed as FLAG-IDA						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£121,648	-£526
Standard of Care	£54,063	0.98				
SA2. Using list price for blinatumomab and inotuzumab received as subsequent induction therapies						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£112,106	-£10,068
Standard of Care	£66,432	0.98				
SA3. Assuming 26 days inpatient stay for administration						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£117,786	-£4,388
Standard of Care	£75,527	0.98				
SA4. No additional mortality risk compared to general population post cure						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£102,625	-£19,549
Standard of Care	£53,203	1.12				
SA5. Using Kurosawa utility values post HSCT (no impact of progression on quality of life post HSCT)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£102,092	-£20,081
Standard of Care	£53,332	1.15				
SA6. Non-parametric survival data with separate survival curves post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£84,065	-£38,109
Standard of Care	£55,047	0.75				
SA1 + SA2 + SA3. Highest cost scenario for standard of care						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£114,000	-£8,174
Standard of Care	£82,782	0.98				
SA4 + SA5. No additional mortality risk and no impact of progression on quality of life post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£83,286	-£38,888
Standard of Care	£53,203	1.36				
SA4 + SA6. Highest survival benefit scenario for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£70,521	-£51,653
Standard of Care	£54,975	0.86				

SA4 + SA5 + SA6. High QALY (survival and quality of life) benefit scenario for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£52,940	-£69,233
Standard of Care	£54,975	0.95				
SA1 + SA2 + SA3 + SA4 + SA6. Highest cost for standard of care and highest survival for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£65,642	-£56,531
Standard of Care	£84,425	0.86				
SA1 + SA2 + SA3 + SA4 + SA5 + SA6. Highest cost for standard of care and high QALY for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£49,278	-£72,895
Standard of Care	£84,425	0.95				

6.3.2.1 Sensitivity to 'cure' point

The ERG parametric base case was used to explore the impact of alternative 'cure' points between 2 and 10 years. Table 35 illustrates that the estimated QALYs decrease as the cure point is increased from 2 to 6 years, and then stabilise for cure points up to 9 years. The ICER is relatively insensitive to changes in the 'cure' point between 2 to 10 years. Once the cure point reaches 10 years, the estimated QALYs begin to increase. This may reflect the point at which the parametric models fit to the *HSCT & Post HSCT* survival data begin to predict survival rates in excess of those observed for the general population.

Table 35: Results of the ERG parametric base case for alternative 'cure' points

Cure point		Costs	QALYs	Inc. cost	Inc. QALYs	ICER
2 years	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£103,125
	SoC	£53,061	0.78			
3 years (ERG parametric base case)	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£114,078
	SoC	£53,165	0.65			
4 years	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£118,018
	SoC	£53,214	0.59			
5 years	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£118,998
	SoC	£53,239	0.57			
6 years	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£118,832
	SoC	£53,253	0.55			
10 years	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£116,209
	SoC	£53,266	0.54			
Not applied	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£89,679

	SoC	£53,202	0.59			

The ERG also calculated the most optimistic sensitivity analysis scenario for the ERG parametric base case (SA1 + SA2 + SA3 + SA4 + SA5 but with post HSCT survival determined by MRD). This resulted in an ICER of £70,931 per QALY gained with inotuzumab compared to standard of care.

6.3.2.2 Other uncertainties

The structure of the company model and manner by which the individual patient survival data were analysed prohibit subgroup analyses. However, in general any patient characteristic that is associated with a reduced likelihood of HSCT (e.g. increased age) is likely to increase the estimated ICER for inotuzumab compared to standard of care.

The cost-effectiveness results are based on the type of patients included in INO-VATE 1022. In patients with poorer prognosis, such as those with two or more prior salvage therapies, and who may have a lower probability of response, the estimated ICER for inotuzumab is likely to be much higher.

The company submission and company model did not allow for inclusion of clofarabine for Ph- patients and TKIs alone or in combination with clofarabine for Ph+ patients as additional comparators. It is uncertain how these comparators compare in terms of costs, remission, survival or quality of life compared to the standard of care arm in INO-VATE 1022.

6.4 Conclusions from ERG analyses

The ERG found inotuzumab to be more costly (cost difference [redacted]) and more effective ([redacted] QALY gain) compared with standard of care. The ERG non-parametric base case ICER was estimated to be £122,174 per QALY gained using a discount rate of 3.5%. The key drivers in the cost effectiveness of inotuzumab are the assumptions concerning the additional benefits of inotuzumab post HSCT.

The ERG adjustments to the model removed some of the problems associated with the predictions from the complex parametric survival models fit separately to each treatment arm in the company base case. The use of a cure point at close to 3 years renders any extrapolation from parametric survival models largely redundant. The size of the ICER is predominantly determined by the choice of how to use of the Kaplan-Meier data post HSCT, and whether these data should be pooled across treatment arms, and/or adjusted for MRD status. Assigning differences in survival in the INO-VATE 1022 post randomisation *HSCT & Post HSCT* sub population attributed to MRD status as an

additional treatment benefit for inotuzumab increases the incremental QALYs estimated for inotuzumab versus standard of care by approximately half of that estimated by assigning all post HSCT differences in survival to inotuzumab. When the model uses parametric survival models based on MRD status, and which predict survival more in line with existing epidemiological data, the choice of a cure point and the use of a cure assumption become less influential. However, the ERG base case excludes a treatment effect for inotuzumab on post HSCT survival as the evidence is highly uncertain, based on the small *HSCT & Post HSCT* sub population from INO-VATE 1022 (patients in the inotuzumab arm and patients in the standard of care arm from the safety population) evaluated post-randomisation.

While costs are also uncertain, particularly given the discrepancy between the standard of care provided in INO-VATE 1022 compared to current NHS practice, these are less impactful on the ICER. Across a range of sensitivity analyses the incremental cost of inotuzumab compared to standard of care remains in the region of . However, depending on the assumptions about the post HSCT survival and quality of life benefits, the incremental QALY gain can vary between and . Existing epidemiological data[16, 17] contradicts the assumption that HSCT is curative as they indicate that individuals with R/R B-cell ALL who survive HSCT do not return to the mortality risks associated with the general population. Epidemiological evidence suggests that patients who survive HSCT may do so with increased morbidity compared to the general population,[26] and in INO-VATE 1022 the majority experienced progression events.

Inotuzumab is more costly and more effective than standard of care, but more evidence is needed to determine whether it offers additional survival benefit beyond increasing the rate of CR/CRi and HSCT. Without evidence that patients who receive HSCT following inotuzumab experience longer survival, and at near to full health, than patients who receive HSCT following standard of care, the ICER for inotuzmab is likely to be greater than £100,000 per QALY.

7 End of life

The life expectancy of adult patients with R/R B-cell ALL is only around three to six months with current salvage therapies, meeting the end of life criterion set by NICE.

The median overall survival was 7.7 months (95% CI: 6.0 to 9.2) in the inotuzumab group and 6.7 months (95% CI: 4.9 to 8.3) in the standard of care group in the INO-VATE 1022 trial, therefore the median difference between inotuzumab and standard of care does not meet the survival benefit required by NICE. While inotuzumab showed little survival benefit in INO-VATE 1022, the economic model predicts an increase in undiscounted survival of over two years, and a discounted QALY gain in excess of 10 months. Although the survival benefits of inotuzumab are subject to high uncertainty, it is likely that by increasing the rate of HSCT, inotozumab could increase in mean survival for patients with R/R B cell ALL by more than 3 months.

The CS stated that the OS data appeared to deviate from the proportional hazards assumption at around 15 months with the separation of curves in the Kaplan-Meier plots appearing after the median had been reached. Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. RMST results were strongly dependent on the choice of truncation time, [redacted]. By 36 months only one patient was included in the analysis from each treatment arm. The RMST analysis results presented in the CS were those for the truncation time of 37.7 months; median OS in the inotuzumab group was 13.9 months (standard error (SE): 1.1) and for SoC 9.9 months (SE: 0.9), with a difference of 3.9 months between groups (95% CI: 1.2 to 6.7). Therefore, if the RMST analysis results at 37.7 months are considered to be reliable, the improvement in survival with inotuzumab exceeds the end of life threshold of 3 months.

While inotuzumab showed little survival benefit in INO-VATE 1022, the economic model predicts an increase in undiscounted survival of over two years, and a discounted QALY gain in excess of 10 months. Although the survival benefits of inotuzumab are subject to high uncertainty, it is likely that by increasing the rate of HSCT, inotozumab will increase the mean survival for patients with R/R B cell ALL by more than 3 months.

The number of patients indicated for inotuzumab treatment in the UK is small. The incidence of B-cell ALL has been estimated to be approximately 1.2 per 100,000 population, based on statistics

provided by Cancer Research UK. It was estimated that the R/R B-cell ALL population for 2017 in England would be 117 patients. Inotuzumab was granted orphan designation by the European Commission on 7th June 2013.

8 Overall conclusions

Evidence from one reasonably good quality RCT demonstrates that inotuzumab is effective at improving remission outcomes, with significantly more patients achieving a complete response or complete response with incomplete count recovery (CR/CRi) than patients receiving standard of care (SoC). Inotuzumab was also 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; RMST results [redacted]. Most treatment emergent adverse events (TEAEs) and Grade ≥3 TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm than the SoC arm. A reasonably high proportion of patients either permanently or temporarily discontinued inotuzumab treatment due to adverse events.

The RCT of inotuzumab only included the subset of patients who were suitable for intensive therapy and were due to receive either Salvage 1 or Salvage 2 therapy, which is only a subset of the anticipated licensed population. No comparative evidence has been presented for the use of inotuzumab in patients who require third or later salvage treatment, or who are not fit for intensive treatment or may be treated with palliative intent.

The key drivers in the cost effectiveness of inotuzumab are 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. The cost-effectiveness model provided by the company allowed for a range of alternative scenarios to be explored. There was weak evidence for survival difference post HSCT based on INO-VATE 1022, and this was [redacted], and should be interpreted with caution. Despite the complexity of the parametric survival models applied in the company model, these proved not to be influential in determining the results. The imposition of a cure assumption for patients surviving three years after HSCT and the predicted survival for the standard of care arm from the company model were not supported by epidemiological evidence.

8.1 Implications for research

Final OS and safety updates from the INO-VATE 1022 trial were expected in March 2017 (although not received by the ERG). In addition, there are a number of ongoing trials of inotuzumab in patients

with ALL, including trials of inotuzumab in combination with other therapies, as described in Section 4.1.7.

There is a lack of evidence examining the clinical effectiveness and safety of inotuzumab in patients who are due to receive salvage therapies beyond Salvage 2, or who would be treated with palliative intent. In addition, there is currently no evidence on the relative effectiveness of inotuzumab and clofarabine-based combination chemotherapy for Ph- patients and TKIs alone or in combination with clofarabine-based chemotherapy for Ph+ patients, which are treatments used in UK clinical practice.

Additional follow up of INO-VATE 1022 is unlikely to provide more evidence to support the nature of any post HSCT survival benefits assumed for inotuzumab, as it was neither designed nor powered to answer such a question. However, additional research into the prognostic value of MRD status following use of monoclonal antibodies to induce remission and bridge to HSCT may offer some support for an additional survival benefit for inotuzumab through its impact on rates of MRD negativity.

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10 Appendices

10.1 Checklist

Table 36 summarises the results of the Phillips checklist applied to the company cost effectiveness submission.

Table 36: Phillips checklist for company submission.

Description of quality	Response (✓,✗ or NA)	Comments	Reference
Structure			
S1 Statement of decision problem objective			
Is there a clear statement of the decision problem?	✓	The decision problem was clearly stated in the first table of the CS using the PICOS framework.	CS, Table 1, p15-17
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	The objective is specified clearly as: "*to determine the clinical and cost-effectiveness of inotuzumab ozogamacin within its anticipated marketing authorisation for adult patients with relapsed or refactory (R/R) B-cell acute lymphoblastic leukaemia (ALL)*". The objective is consistent with the decision problem and the final scope issued by NICE.	CS, p14
Is the primary decision-maker specified?	✓	Yes, NICE.	
S2 Statement of scope/perspective			
Is the perspective of the model clearly stated?	✓	Yes, the perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS).	CS, Table 1, p15-17
Are the model inputs consistent with the stated perspective?	✓	Yes.	
Has the scope of the model been stated or justified?	✓	The scope set by NICE and that used for the company's de novo analysis was clearly stated in the first table of the CS.	CS, Table 1, p15-17
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	Outcomes relate to life-years, quality adjusted life years based on EQ-5D and costs.	
S3 Rationale for structure			

Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	×	The decision model is based on a partitioned survival approach with separate health states across CR/CRi and HSCT outcomes. Tunnel states reflected the waiting period for HSCT and separate sub-states represented progression-free and progressed disease. The main goal in ALL treatment is to bridge patients to potentially curative therapy (i.e. HSCT). The absence of any explicit structural link in the model between remission outcomes (CR/CRi) and HSCT (and hence the proportion of patients within each of the main initial health states) omits the relationship specific to patient characteristics and subgroups on state membership.	CS, p159-166
Are the sources of data used to develop the structure of the model specified?	×	The model was designed in line with the NICE reference case, from the perspective of the UK NHS and PSS. No details were provided in the main submission concerning the model conceptualisation process and the role of experts in validating the final model structure. The manufacturer had received advice from an advisory board meeting surrounding a previous model.[9]	CS, p159-166
Are the causal relationships described by the model structure justified appropriately?	✓	The causal relationship was justified, although the causal relationship between inotuzumab and post-HSCT is highly uncertain.	CS, p159
S4 Structural assumptions			
Are the structural assumptions transparent and justified?	✓	Yes.	CS, Table 72 – p241-243
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	×	No. The structure prevents the exploration of subgroups based on patient characteristics that could also influence likelihood of HSCT. The use of a "cure" point was not supported in external epidemiological data.	
S5 Strategies/comparators			
Is there a clear definition of the options under evaluation?	✓	Yes.	CS, p51-53
Have all feasible and practical options been evaluated?	×	Comparators not evaluated from the NICE scope include: • palliative/best supportive care • clofarabine • TKIs alone.	
Is there justification for the exclusion of feasible options?	✓	**Palliative/best supportive care**: *"In the proposed draft label, inotuzumab ozogamicin is not only intended for use in patients who can tolerate chemotherapy or proceed to potentially curative therapy (e.g., hematopoietic stem cell transplant [HSCT]). However, patients being treated with palliative intent (e.g., patients receiving steroids, pain control, etc.) would not be expected to receive inotuzumab ozogamicin in NHS practice."* **Clofarabine**: *"Key clinician expert opinion has indicated that clofarabine is used off-label in an*	CS, p167 and company response to clarifications, question A2 - p4

		estimated 10–15% of 18–30 year olds in the UK. As this use is off-label, it is not appropriate to compare to inotuzumab within this submission." **TKIs alone**: "*There is uncertainty how effective TKIs are after further lines of treatment, and there are limited efficacy data to inform the model; therefore, only the costs of TKIs have been incorporated for these patients, and efficacy remains the same as SoC."*	
S6 Model type			
Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	✓	Yes.	
S7 Time horizon			
Is the time horizon of the model sufficient to reflect all important differences between options?	✓	The time horizon used in the model was 60 years, which is assumed to represent a lifetime horizon.	CS, Table 41 – p165
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	**Time horizon:** The time horizon is in line with NICE guidance. **Duration of treatment:** The schedule of treatment used in the model is consistent with the draft marketing authorisation (Section 3.2). **Duration of treatment effect:** Inotuzumab was justified as having a treatment effect over a patients' lifetime from having "*statistically significant and clinically meaningful improvements in MRD negativity*".	CS, p165 & p259
S8 Disease states/pathways			
Do the disease states or the pathways reflect the underlying biological process of the disease in question and the impact of interventions?	✓	The four main health states in the model capture unique biological states in the ALL pathway. The company assumed response status was determined within the initial cycle of treatment and that inotuzumab determined state membership and outcomes within each health state using the INO-VATE 1022 trial. The ERG have doubts surrounding the pathway between remission status (CR/CRi) and HSCT (S3) and the extent of the treatment effectiveness post HSCT (S7).	
S9 Cycle Length			
Is the cycle length defined and justified in terms of the natural history of disease?	✓	The cycle length was set at 28 days in the model, which was "*broadly in line with the treatment cycle length of inotuzumab and comparator regimens"*.	CS, p160
Data			
D1 Data identification			

Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Yes	CS, Sections 3.1, 5.1, 5.4.3, 5.5.1.
Where choices have been made between data sources, are these justified appropriately?	✓	Due to limited sources of data this was not a significant issue. However, in instances when alternative sources were available justifications were made (e.g. GvHD unit costs) and sensitivity analyses conducted between key sources (e.g. post-HSCT utilities).	CS p234 & 213. See CS Table 72 for summary.
Has particular attention been paid to identifying data for the important parameters in the model?	×	Insufficient attention was given to identifying data for the long-term survival post HSCT or for the role of MRD status.	
Has the quality of the data been assessed appropriately?	✓	**Clinical Effectiveness:** *"A descriptive quality assessment of the included randomised controlled trials (RCTs) was performed by two independent reviewers using comprehensive assessment criteria based on the recommendations in the NICE manufacturer's submission template and the quality assessment of the included non-RCTs was performed using a checklist by Downs and Black."* (Evidence submission, page 66) **Cost Studies:** "*Quality checks of studies providing data for cost and resource use were undertaken using the NICE critical appraisal for RCTs169 and the Downs and Black checklist for non-RCTs.*" **HRQoL Studies**: "*Quality assessment of the included studies was carried out using the Papaioannou et al checklist, and the results presented in Appendix 8.4"*	CS p66, 206 & 220.
Where expert opinion has been used, are the methods described and justified?	×	Expert opinion has been sought throughout the CS, however no details were provided concerning the methods used, the specific questions asked.	
D2a Baseline data			
Is the choice of baseline data described and justified?	✓	Yes.	
Has a half-cycle correction been applied to both cost and outcome?	✓	Yes.	CS, p160
D2b Treatment effects			
If the relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	×	In part. Treatment effects for two of the health states are based on a randomised comparison. A treatment effect for post HSCT survival is evaluated post randomisation.	CS, p170-173

Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	Each covariate used was justified appropriately (CS, Table 45) and the choice of parametric curve was informed through visual inspection, assessment of clinical plausibility, and metrics of statistical fit in line with NICE Decision Support Unit guidelines.	CS, p170-173
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	See S7 (duration of treatment).	CS, p259
Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	Yes.	CS, Table 83
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis.	✓	Pooled post HSCT survival with MRD covariate and pooled post HSCT was explored in the CS and points for clarification respectfully.	CS, Table 83 & company response to clarifications, question B4 p74-77
D2c Costs			
Are the costs incorporated into the model justified?	✓	Yes.	
Has the source of the costs been described?	✓	Unit costs were based on the literature, the company's proposed list price, NHS Reference costs, the monthly index of medical specialties (MIMS) and the Department of Health's electronic market information tool (eMit). Where appropriate, unit costs were inflated to 2015/2016 prices. All sources were explicitly stated and described.	CS, Section 5.5
Have the discount rates been described and justified given the target decision maker?	✓	The company has given justification for using a discount rate of 1.5% in the UK decision making context as follows: "*To minimise the differential impact of discounting on costs and benefits, the NICE Methods Guide states that in such cases when treatment restores people who would otherwise die to near full health over a very long period, a lower discount rate of 1.5% may be considered.*" Conventional 3.5% discount rates were presented as a scenario.	CS, p27
D2d Quality of life weights			
Are the utilities incorporated into the model appropriate?	✓	Yes, although age adjustment was not applied in the base case.	CS, Section 5.4
Is the source of the utility weights referenced?	✓	All sources are referred and described.	CS, Section 5.4

Are the methods of derivation for the utility weights justified	✓	Treatment specific utilities applied to the No CR/CRI & no HSCT and CR/CRi & no HSCT health states were derived from EQ-5D data taken within the pivotal trial and used the UK value set for calculation.	CS, p198
D3 Data incorporation			
Have all data incorporated into the model been described and referenced in sufficient detail?	✓	All data are referred and described.	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	NA		
Is the process of data incorporation transparent?	✓	Data is referenced explicitly in the company's model and incorporated with the value and as the distributions mentioned in appendix 10 of the CS.	CS, appendix 10
If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	✓	The chosen distributions has been described (see above) but not justified.	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Yes, parameter uncertainty has been adequately addressed by the company. However, the company also included first order uncertainty in patient characteristics.	
D4 Assessment of uncertainty			
Have the four principle types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been justified?	✓	See below.	
D4a Methodological			
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	The effect of alternative relevant discount rates has been addressed along with the impacts of different dosing methods to that used in the base case (methods of moments) and the application of the half cycle correction.	
D4b Structural			
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	A wide range of scenarios and sensitivity analyses were conducted which provided meaningful evidence of the key drivers of cost-effectiveness and areas of uncertainty in the base case model.	
D4c Heterogeneity			
Has heterogeneity been dealt with by running the model	×	The final scope did not specify specific populations and subgroups. The impact of covariates is	

separately for different subgroups?		presented as part of exploratory analyses but the structural issues inhibit their usefulness.	
D4d Parameter			
Are the methods of assessment of parameter uncertainty appropriate?	✓	In line with the NICE reference case deterministic sensitivity analyses were performed on a series of model parameters. Probabilistic sensitivity analyses were also performed.	
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	All range data is reported and incorporated as distributions.	
Consistency			
C1 Internal consistency			
Is there any evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	The technical accuracy of the calculations of costs and QALYs within the model was verified by the developers of the model on behalf of the company. In addition, several (unspecified) quality control measures were undertaken and an independent modeller critiqued the structure, parameter inputs, and core assumptions (see Section 5.2.10).	
C2 External consistency			
Are any counterintuitive results from the model explained and justified?	✓	The probabilistic ICER is significantly higher.	
If the model has been calibrated against independent data, have any differences been explained and justified?	×		
Have the results of the model been compared with those of previous models and any differences in results explained?	×		

10.2 ERG Alternative Scenarios (1.5% Discount rate)

Table 37 shows the results of the ERG corrections and adjustments using a discount rate of 1.5% for costs and outcomes. Table 38 summarises the sensitivity analysis for the ERG non-parametric base case using the lower discount rate of 1.5%.

Table 37: Results of the relevant scenarios and additional calculations for the ERG base cases (1.5% discount rate)

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change from company ICER
Company base case results - deterministic (1.5% discount rate)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£40,013	n/a
Standard of Care	£66,433	0.54				
1. Fix from CS response						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£39,949	-£64
Standard of Care	£66,613	0.54				
2. Parametric survival functions: pooled survival with MRD ('cure' point 3 years post HSCT)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£56,819	+£16,806
Standard of Care	£64,383	0.92				
3. Age adjusted utilities						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£43,909	+£3,896
Standard of Care	£66,433	0.52				
4. Chemotherapy costs in line with INO-VATE						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£41,021	+£1,008
Standard of Care	£63,945	0.54				
5. Pooled on treatment utilities						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£40,076	+£63
Standard of Care	£66,433	0.54				
6. Subsequent therapy costs in line with chemotherapy						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£44,082	+£4,069
Standard of Care	£52,899	0.54				
7a. Non-parametric survival data with pooled post-HSCT survival						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£61,021	+£21,008

Standard of Care	£64,580	1.55				
7b. Non-parametric survival data with separate survival curves post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£40,550	+£614
Standard of Care	£66,288	1.12				
8. Fourfold increase in risk of mortality compared to general population post-cure						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£53,069	+£13,056
Standard of Care	£66,456	0.49				
9. Weighted average NHS administration costs and length of inpatient stay						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£41,389	+£1,376
Standard of Care	£70,990	0.54				
ERG non-parametric base case: 1 + 3 + 4 + 5 + 6 + 7c + 8 + 9						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£97,988	+£57,975
Standard of Care	£53,332	0.98				
ERG parametric base case 1 + 2 + 3 + 4 + 5 + 6 + 8 + 9						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£90,982	+£50,969
Standard of Care	£53,713	0.75				

Table 38: Sensitivity analysis for ERG non-parametric base case using a 1.5% discount rate

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change from base case ICER
ERG non-parametric base case results - deterministic (1.5% discount rate)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£97,988	n/a
Standard of Care	£53,949	1.17				
SA1. All standard of care costed as FLAG-IDA						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£97,568	-£420
Standard of Care	£54,063	1.17				
SA2. Using list price for blinatumomab and inotuzumab received as subsequent induction therapies						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£89,954	-£8,034
Standard of Care	£67,049	1.17				
SA3. Assuming 26 days inpatient stay for administration						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£94,486	-£3,502

Standard of Care	£76,144	1.17				
SA4. No additional mortality risk compared to general population post cure						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£76,539	-£21,449
Standard of Care	£53,849	1.44				
SA5. Using Kurosawa utility values post HSCT (no impact of progression on quality of life post HSCT)						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£82,619	-£15,369
Standard of Care	£53,949	1.39				
SA6. Non-parametric survival data with separate survival curves post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£65,978	-£32,010
Standard of Care	£55,613	0.87				
SA1 + SA2 + SA3. Highest cost scenario for standard of care						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£91,465	-£6,523
Standard of Care	£82,782	0.98				
SA4 + SA5. No additional mortality risk and no impact of progression on quality of life post HSCT						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£62,716	-£35,272
Standard of Care	£53,849	1.76				
SA4 + SA6. Highest survival benefit scenario for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£51,408	-£46,580
Standard of Care	£54,975	0.86				
SA4 + SA5 + SA6. High QALY (survival and quality of life) benefit scenario for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£39,068	-£58,920
Standard of Care	£54,975	0.95				
SA1 + SA2 + SA3 + SA4 + SA6. Highest cost for standard of care and highest survival for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£47,875	-£50,113
Standard of Care	£85,008	1.06				
SA1 + SA2 + SA3 + SA4 + SA5 + SA6. Highest cost for standard of care and high QALY for inotuzumab						
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£36,383	-£61,605
Standard of Care	£85,008	1.17				

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 27 April 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Comparators in the NICE Scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 11 the ERG states: *"However, some of the comparators listed in the NICE scope (clofarabine-based combination chemotherapy for Philadelphia chromosome (Ph) negative patients and tyrosine kinase inhibitors (TKIs) alone or in combination with clofarabine-based chemotherapy for Ph positive patients) were not included in the submission; these treatments are used in UK clinical practice so should have been included as comparators in the CS."*	Clarity should be provided that these treatments are rarely used in clinical practice, as put forward in the company submission *i.e.* clofarabine is used off-label in an estimated 10-15% of 18 to 30-year old patients in the UK and there is limited efficacy data to support the use of TKIs beyond first-line treatment.	The current statement makes no distinction between the treatments in terms of how frequently they would be used in clinical practice, and does not point out that clofarabine use would be off-label and that there is limited evidence to support the use of TKIs in this population, which could be misleading to an uninformed reader. This is mentioned in Appendix 10.1 of the ERG report, but not within the main body of the text. Clarity should be added to the main body of the report for consistency and as this is important information.	Not a factual inaccuracy, these treatments are used in UK clinical practice.
On page 17 and page 57, the ERG states: *"… whereas two treatments that are used in NHS practice were not used as comparators within the trial."*			
Page 70 – ERG comment: *clinical advice received by the ERG was that clofarabine is used in UK clinical practice and is efficacious,*	Further clarification requested on the advice received by the ERG, namely in what age group clofarabine is used, and the	Without further details around the advice, the stated use of clofarabine could be misleading, if indeed it is only used in children or	Not a factual inaccuracy, clinical advice was that clofarabine is used in the adult population in UK clinical

therefore, should have potentially been a comparator in the submission.	proportionate use across the adult population in the UK. Advice to Pfizer stated that clofarabine is only really used in young adults (<30), off label, and children, and is calculated to only apply as a comparator to 5% of the patient population in this appraisal (detailed in page 167 in the CS).	a small subset of the population (e.g. young adults)	practice.

Issue 2 HRQL results

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
On page 13, page 54 and page 57, the ERG states: *"The data presented indicated a greater 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 (although the difference was only statistically and/or clinically significant for a few dimensions)."*	This statement should be amended to specify the domains for which there was a statistically and/or clinical significant difference: *"The data presented indicated a greater 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. Patients receiving inotuzumab were observed to have significantly better appetite, were significantly more ambulatory, and experienced significantly less*	The current statement does not specify the domains in which patients are most likely to benefit and therefore misses some important information.	Not a factual inaccuracy.

	impact on family and social life (estimated mean treatment difference >5 points, p<0.05). They were also statistically significantly more able to perform strenuous activities, basic living needs, work, other daily activities, hobbies, and other leisure activities. Global health status/QoL, dyspnoea, and fatigue [redacted] *."*		
On page 15, the ERG states: *"Limitations in reporting patient-reported outcomes, in terms of the number of patients who completed questionnaires after treatment and the lack of reporting of actual quality of life scores, mean that these results should be interpreted with caution. The open label nature of the trial introduces potential bias for subjective endpoints."* On page 54, the ERG states: *"Completion rates were adequate (the proportion of patients in the trial who completed the*	The summary of patient reported outcomes (page 15 of the ERG report) and the conclusions of the patient reported outcome results section should be made consistent with what is presented within the results (page 54). As stated below, the actual patient reported outcome scores are also presented within the CS (Table 29), so this section should be amended to account for these results.	There are currently some differences between what is stated in the summary and conclusions and what is presented within the results section.	Not a factual inaccuracy. The completion rates reported in the CS [redacted] were adequate. However, the actual number of patients who completed questionnaires after treatment was not reported. The scores reported in Table 29 were 'overall treatment comparisons for the ITT population using longitudinal mixed-effects models with random intercepts and slopes with treatment, time, treatment-by-time interaction, and

questionnaires), although the number of patients who remained on treatment decreased considerably after the first cycle of treatment, therefore the number of patients completing the questionnaires reduced; the actual numbers of patients completing the questionnaires was not reported." In the conclusion to this section, on page 54, and in the overall conclusions on page 57, they state: *"limitations in reporting, in terms of the number of patients who completed questionnaires after treatment and the lack of reporting of actual quality of life scores after treatment…"*			baseline scores as covariates', rather than actual quality of life scores post-treatment or change from baseline scores.

Issue 3 Criteria for including studies in the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14 the ERG states: *"…the criteria used in the systematic review were broader than those required for the submission; therefore, only studies specifically of interest to the NICE scope would be included. The specific eligibility criteria for inclusion in the submission were not stated, therefore, cannot be checked for appropriateness."*	As specified in the CS and the response to the ERG question A5, the criteria for inclusion in the submission were defined by the NICE scope.	The inclusion criteria for relevant evidence for the submission. Table 8 in the CS presents the inclusion criteria, which covers the interventions, population and outcomes in the scope. It is thus suggested to amend this wording to reflect this.	Not a factual inaccuracy. Specific inclusion/exclusion criteria were not presented for the submission. Table 8 presents eligibility criteria for the broader review, which includes interventions that were not eligible for inclusion in the submission.
On page 30, the ERG states: *"The eligibility criteria for the submission were not stated so cannot be checked for appropriateness."*			

Issue 4 Subsequent HSCT results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14 and page 57, the ERG states: *"In addition [redacted] inotuzumab*	Suggest changing to: *"In addition, [redacted]% of inotuzumab patients and [redacted]%*	The current statement may be misleading and it should be emphasised that this statement	Sentence amended on pages 14 and 56 as follows: "In addition [redacted] inotuzumab

patients and [redacted] SoC patients did not receive HSCT, despite achieving CR/CRi"	*of SoC patients who achieved CR/CRi did not receive HSCT."*	only applies to those patients that achieved CR/CRi and are not referring to the overall population. In addition, it is important to note that there may be other reasons for why a patient may not receive HSCT. These may include (but are not limited to) age, donor suitability, presence of infection, patients no longer in remission by the end of treatment. It is suggested for full information, this is also reflected in the text.	patients and [redacted] SoC patients who did not receive HSCT achieved CR/CRi". On pages 14 and 57 it is already acknowledged that the decision to perform HSCT is complex. The suggested text is incorrect ([redacted] inotuzumab patients and [redacted] SoC patients who achieved CR/CRi did not receive HSCT).

Issue 5 RMST analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

On page 15, the ERG states: *"The OS data were subject to some limitations. RMST results were* [redacted] *The RMST analysis results presented in the CS were those for the truncation time of 37.7 months. The median OS presented for the SoC group was considerably higher than other estimates of OS, presented in Table 6 of the CS (range 3 to 5 months), suggesting that the RMST analysis appears to inflate OS."* On page 49 and page 57, the ERG states: *"However, the median OS presented for the SoC group was considerably higher than other estimates of OS, presented in Table 6 of the CS (range 3 to 5 months), suggesting that the RMST analysis appears to inflate OS."*	Remove the comparison between RMST and median outcomes.	It is not suitable to compare medians and RMST results, as they represent different things. In this case, due to non-proportional hazards, we believe that the RMST analysis is a more accurate reflection of the true treatment effects. Table 6 is only presented within the submission to provide a summary of OS results with regards to end-of-life criteria, and was not intended for comparison between the different results. It may be the case that the ERG disagree with this conclusion, instead believing that median OS is most appropriate. However, it is not appropriate to compare the results as they have done here. This implies the two numbers are alternate representations of the same thing, which is not the case. It is more suitable to consider which is the most appropriate method to use within the specific situation, and which method would be expected to most accurately reflect what is occurring. The ERG should frame their commentary as such, so as to not be misleading.	Not a factual inaccuracy.

Issue 6 Addition of wording for clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 36, within the section "Trial Drugs", the sentence: *"Patients who achieved CR could undergo HSCT at the investigator's discretion"* references CR but should reference CR/CRi.	Change CR to CR/CRi	Increase clarity of sentence	This table was copied directly from the CS (Table 11), therefore this was an error in the CS, not a factual inaccuracy in the ERG report. However, we have corrected it on page 36 of the ERG report.
On page 36, within the section "Trial Drugs", the sentence *"…received HSCT without either CR or CRi"* requires more clarity on those proceeding to HSCT.	Change the end of the sentence from *"…received HSCT without either CR or CRi" to* *"…received HSCT without either CR or CRi with study treatment (these patients more commonly received a new induction therapy before proceeding to HSCT)."*	Patients who achieved CR or CRi could undergo HSCT at the investigator's discretion. Patients who did not achieve CR/CRi in some cases did go to HSCT, but more commonly went on to receive a new induction therapy before proceeding to HSCT.	This table was copied directly from the CS (Table 11), therefore it is not a factual inaccuracy in the ERG report. However, we have amended page 36 of the ERG report, as suggested.
On page 38, within the section "Major Secondary Outcomes", it is suggested to add *"CR/CRi"* to *"complete remission"* for clarity	Change *"…among those who achieved complete remission" to* *"…among those who achieved complete remission (CR/CRi)"*	Increase clarity of sentence	This table was copied directly from the CS (Table 11), therefore it is not a factual inaccuracy in the ERG report. We do not consider that the suggested amendment is required.

On page 40, within the section "Pre-planned subgroups", it is suggested to add *"per CRF"* to *"Duration of first remission"*	Change *"Duration of first remission" to* *"Duration of first remission (per CRF)"*	Increase clarity of sentence	This table was copied directly from the CS (Table 11), therefore it is not a factual inaccuracy in the ERG report. We do not consider that the suggested amendment is required.
On page 50, in the Section OS according to baseline patient characteristics, it states: *"…had no Grade 3+ adverse events and had not received a previous HSCT".* This should specify Grade 3+ hepatic adverse events / Grade 3+ infectious adverse events	Replace *"Grade 3+ adverse events"* with *"Grade 3+ hepatic/infectious adverse events*"	Increase clarity of sentence	Sentence on page 50 amended, as suggested.
On page 51, it states: *"…[redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi".* It should be noted this statement refers to with the study treatments. Repeated again in final paragraph of page 56.	Add "*…with study treatment"* to end of sentence so it reads: "…*despite not achieving CR/CRi with study treatment.* " (also make amend to final paragraph of page 56)	Increase clarity of sentence	The suggested amendment is not required, as the next two sentences provide clarity.

Issue 7 Clarification of population numbers in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 41, the ERG states: *"Sixty-three percent of patients in the SoC arm received FLAG-based chemotherapy, 23% received CM and 14% received HIDAC."* Could the ERG confirm which dataset is being used to derive these figures? Also an issue on page 67.	Suggested that correct numbers would be the safety population (n=143), which is FLAG 65% (93 /143), CM 23% (33 /143), and HIDAC 12% (17/143)	Increase clarity of source, or change text	Page 41: No amendment required, this section describes the full trial, rather than the safety population. The figures are from Table 10 of the CS and also in the summary box on page 62 of the CS. Page 68: Amendment recognized. "Hence, approximately two thirds (65%) of patients were assumed to receive FLAG and 23.08% and 11.89% of patients were assumed to receive CM and HIDAC, respectively (safety population)."

Issue 8 Clarification of numbers in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 41, the ERG states: *"The safety population (also called the modified ITT (mITT) population) included all randomised patients who received at least one dose of study drug by 2 October 2014."* However the cut-off date is incorrect for this population.	Replace date with cut-off for mITT (08 March 2016)	This 2nd October 2014 date is the cut-off date for the first analysis of CR/CRi (ITT218 patient population), not the ITT or mITT population.	This was not clear in the CS, however, we have corrected this on page 41 of the ERG report.

Issue 9 Edits to Table 2, page 42

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 2, the age is not reported for the ITT218, however this data is available if required: 46.2 years (SD 17.87) and 45.8 years (SD 16.6) for the inotuzumab and SoC arms, respectively.	Can replace NR with 46.2 years (SD 17.87) and 45.8 years (SD 16.6) for the inotuzumab and SoC arms, respectively.	Additional information, not reported in Table in company submission.	Not a factual inaccuracy.
In Table 2, the previous HSCT from the ITT population is cited as 28 and 26 in the inotuzumab and SoC arms, respectively. This	Replace 28 with 29, and 26 with 31, as per Figure 16 in the company submission. Source: sCSR table 14.2.2.6.2	Correction of typo on numbers, carried through from company submission.	This was an error in the CS, not a factual inaccuracy in the ERG report. However, we have corrected it on page 42

should be 29 and 31.			of the ERG report.
Page 44, text states *"The average age…"* but suggested to replace with *"median"* for clarity	Replace *"The average age…"* with *"The median age…"*	Clarity of text	Not a factual inaccuracy.

Issue 10 Typo in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, section 4.2.3 *Summary of the results of the included trials*, 316 patients are cited instead of 326	Replace 316 with 326	Typo in text	Corrected on page 44 of the ERG report.

Issue 11 p-value for difference in MRD-negativity in CR/CRi patients between arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 45, Table 3, the p-value for MRD negativity in CR/CRi patients between arms is not reported, however statistic is available ([redacted]).	Suggest to replace NR with [redacted] *(reference sCSR, Table 39)*	Additional information	Not a factual inaccuracy.

Issue 12 Prespecified boundary for OS analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, when discussing overall survival, the ERG cite *"…at a prespecified boundary of p=0.0208."* Suggested to state that this is the 2-sided alpha	Add *"(2-sided alpha)"* at end of sentence	The prespecified boundary was 0.0104 (1-sided alpha), or 0.0208 (2-sided). Text should specify this (*i.e.,* 2-sided).	Sentence on page 47 amended, as suggested.

Issue 13 Safety results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 55, the ERG states: [redacted]	This should be amended to: [redacted]	The most common TEAEs are reported when occurring in greater than [redacted]% of patients. (If it were [redacted] patients then additional TEAEs may also need to be presented).	Corrected on page 54 of the ERG report.
On page 55, the ERG states: [redacted]	Suggest amending to: [redacted]	Provides clarity on the number of events of neutropenia and removes any ambiguity.	Not a factual inaccuracy.

[redacted]	[redacted]		

Issue 14 Missing citation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The search strategies were generally appropriate, although a secondary publication of one of the studies included as non-RCT evidence, appears to have been missed by the searches	The study was identified in the SLR (citation id 3376).	It was a single arm study and the scope of SLR was restricted to comparative studies only. Therefore, this study was excluded at secondary screening stage	Not a factual inaccuracy. There was no way of telling for definite whether the searches missed this publication, as there was no list of excluded studies presented. This publication 'appeared' to have been missed, as it was not listed in Table 9, along with the other secondary references for studies included in the submission.

Issue 15 SLR search terms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A possible typing error was identified in the search	Further clarification	No additional studies were retrieved for any of clinical and	Not a factual inaccuracy.

strategies: lympholeuci* would have been more appropriately truncated as lympholeuc*.		economic SLR if we replace lympholeuci* with lympholeuc*	

Issue 16 Missing citation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The electronic searches appear to have missed a publication by Kantarjian et al. in 2012; this publication presented the results of part 1 of the NCT01363297 study that was included in the CS as supporting evidence	The study was identified in the SLR (citation id 3376).	It was a single arm study and the scope of SLR was restricted to comparative studies only. Therefore, this study was excluded at secondary screening stage	Not a factual inaccuracy. There was no way of telling for definite whether the searches missed this publication, as there was no list of excluded studies presented. This publication 'appeared' to have been missed, as it was not listed in Table 9, along with the other secondary references for studies included in the submission.

Issue 17 SLR search terms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The search strategies for MEDLINE, EMBASE and the Cochrane Library contain a set of terms to limit the results to UK studies. However, a fairly	Further clarification	The addition of terms "GB:ab,ti OR U.K. OR G.B." gives 19 additional studies, none of which are relevant from a cost and resource use review	Not a factual inaccuracy.

narrow range of textwords for the UK is used. Further synonyms could have been included to improve the sensitivity of this search, for example GB, “G.B.”, “U.K.” and also the inclusion of the countries that make up the UK and major UK cities.		perspective. However, England, Scotland, Wales, and Northern Ireland as separate terms were not searched. The addition of “England OR Scotland OR Wales OR 'Northern Ireland' OR 'Northern Ireland'/syn” terms provide 27 additional studies however, none of the studies are relevant from cost and resource use review perspective	

Issue 18 Safety data set figures

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 of the ERG report states that the safety dataset excludes [redacted] of the 164 patients randomised to the investigators choice arm.	Correct to [redacted] out of 162 patients.	ITT population in the SOC arm is 162	Amendment recognised: “The use of the safety dataset (also referred to as the modified ITT dataset) excludes [redacted] of the 162 patients randomised to the investigator’s choice arm.”

Issue 19 Health state numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 - Health state numbers incorrect	ERG included the following: HSCT & Post HSCT (n = [redacted] on inotuzumab and [redacted] on standard of care)	HSCT & Post HSCT (n=[redacted] on inotuzumab and [redacted] on standard of care)	Amendment recognised: "HSCT & Post HSCT (n = [redacted] on inotuzumab and [redacted] on standard of care)"

Issue 20 Incorrect reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23, the sentence "[redacted]" is referenced in relation to the SPC. This is in fact from the INO-VATE 1022 trial protocol.	Change reference to trial protocol	Reference incorrect	This information was copied from the SPC (page 3), not the INO-VATE 1022 trial protocol, therefore, no amendment required.
Page 86 – Incorrect reference	The ERG commented that with R/R Ph-negative ALL patients(2) reported survival data based on 1,706 patients	This corresponding reference is the Kantarjian inotuzumab paper, and doesn't reflect the numbers reported within the report	Amendment recognised. On second inspection the correct reference was deleted causing a referencing error on three pages of the ERG report (pages 20, 85 and 89). The

			corresponding reference should be: Gokbuget N, Dombret H, Ribera JM, Fielding AK, Advani A, Bassan R, et al. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. Haematologica. 2016;101(12):1524-33. This reference is now referred to specifically within the text where appropriate in the FAC page alterations in the addendum.
Page 90 – Incorrect reference	Gokbuget et al(2)	The corresponding reference is the Kantarjian inotuzumab paper, and not Gokbuget	Amendment recognised. See above for correct reference.

Issue 21 Benefit of InO on CR/CRi alone

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113 – Table 27	The ERG presents ICER estimates based on CR/CRi absent of rates of HSCT (HSCT	To ensure accuracy in the interpretation of these results,	Not a factual inaccuracy.

	rate set to zero). Technically this may underestimate the overall survival of the total population of patients who achieved CR/CRi. This is because patients who achieved CR/CRi but did not go on to receive HSCT potentially did so because they had a worse prognosis than those who achieved CR/CRi but did receive a HSCT in INO-VATE. Converging all CR/CRi patients to that same, lower rate of survival lowers the QALY gain and increases the ICER. Further information is requested here to ensure accurate interpretation of the analyses.	suggested to include further explanation of the ERG's analysis so it is clear what has been done and how it may result in an underestimate of survival	

The CS presented supporting evidence from two non-RCT studies; study NCT01363297 and the MDACC study. The results were not as favourable in these studies as in the INO-VATE 1022 trial. However, both studies included patients who received inotuzumab as Salvage 3 or later therapy, therefore, patients in these studies had a poorer prognosis than those in the INO-VATE 1022 trial.

1.1 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS described a systematic review of comparative studies of patients aged 15 or over with R/R ALL receiving a range of pharmacological treatments compared with another of the treatments listed, placebo or best supportive care. However, the CS stated that the criteria used in the systematic review were broader than those required for the submission; therefore, only studies specifically of interest to the NICE scope would be included. The specific eligibility criteria for inclusion in the submission were not stated, therefore, cannot be checked for appropriateness.

The search strategies were generally appropriate, although a secondary publication of one of the studies included as non-RCT evidence, appears to have been missed by the searches. However, it is unlikely that any relevant RCTs of inotuzumab have been missed.

The methods of the INO-VATE 1022 trial were described in adequate detail and the quality of the trial was assessed using appropriate criteria; the trial was reasonably good quality. However, some of the results were not presented in sufficient detail; the ERG requested additional data from the Company, which were provided. Data presented for the two non-RCT studies were limited and the results of the quality assessment were not presented.

The results of the INO-VATE 1022 trial relating to CR/CRi are likely to be reliable; whilst remission outcomes were assessed by unblinded study personnel, the results for the full ITT population were similar to those of the smaller ITT218 population, whose remission outcomes were assessed by an independent Endpoint Adjudication Committee (EAC).

The results relating to the higher proportion of inotuzumab patients proceeding to HSCT are also likely to be reliable, although [redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice, where patients have to have achieved CR/CRi to be eligible for HSCT. The economic model grouped all HSCT patients together, regardless of CR/CRi status. In addition [redacted] inotuzumab patients and [redacted] SoC patients who did not receive HSCT achieved CR/CRi; the ERG's clinical advisor stated that the decision to perform HSCT is complex; this complexity reflects the need to use hard clinically meaningful endpoints, such as overall survival.

2 Background

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem was appropriate and relevant to the decision problem under consideration. 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 a rare disease in adults, who account for only around 40% of ALL cases, but about 80% of ALL deaths. Around three quarters of ALL patients have disease derived from precursor B-cells (B-cell ALL), although there is some inconsistency within the company submission (CS), with figures of 75% and 82% reported, for the proportion of ALL patients whose disease is derived from precursor B-cells. B-cell ALL is further classified by Philadelphia chromosome (Ph) status; the majority of adults under the age of 60 with B-cell ALL have Ph negative (Ph-) disease. Ph positive (Ph+) disease is associated with poorer outcomes.

The CS stated that approximately 44% of adults with B-cell ALL are expected to relapse, and a further 4% are found to be treatment refractory. The only potentially curative treatment option is haematopoietic stem cell transplant (HSCT), although this is only available to patients who achieve a complete remission (CR) or complete remission with incomplete count recovery (CRi) to chemotherapy-based regimens and for whom a suitable donor can be found. Prognosis for relapsed or refractory (R/R) B-cell ALL is poor, with 5-year overall survival (OS) estimated to be less than 10%. The CS reported that survival following relapse may be as low as three months with current salvage therapies, which have low rates of CR/CRi and, therefore, few patients (5-30%) progress to further potentially curative therapies, whilst survival for patients who receive HSCT is over fourteen months. Survival rates are higher in patients who achieve CR/CRi at first salvage than patients who achieve CR/CRi at second or later salvage. A recently published international reference analysis of outcomes in adults with R/R Ph-negative ALL reported survival data based on 1,706 patients (including 1,416 patients with information on HSCT status).[Gokbuget et al 2016] Overall survival at 36-months was reported to be 11% in the overall population (including patients who did and did not receive HSCT) and exceeded 20% in patients who received HSCT following first salvage treatment.

The CS reported that the incidence of B-cell ALL is approximately 1.2 per 100,000 population, based on statistics provided by Cancer Research UK. The population of interest in the CS is adult patients with R/R B-cell ALL. It was estimated that the R/R B-cell ALL population for 2017 in England would be 117 patients. These figures appear reasonable.

Table 1: Summary of INO-VATE 1022 methodology

Study	INO-VATE 1022
	employees directly involved in the conduct of the study • Participation in other studies involving investigational drug(s) (Phase I-IV) within 2 weeks from randomisation to EOT visit • Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration or may have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study
Settings and location where the data were collected	Project management, data management, clinical monitoring, site monitoring, data programming, and medical writing were performed by ICON plc. Biostatistical analyses were performed by ICON. This study used an external Data Monitoring Committee (eDMC), an external Hepatic Events Adjudication Board (HEAB) and an Endpoint Adjudication Committee (EAC).
Trial drugs	**InO:** Patients received inotuzumab at a starting dose of 1.8mg/m^2 per cycle (0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15). Cycle 1 lasted for 21 days, up to 28 days if necessary for toxicity recovery, and each subsequent cycle lasted for 28 days. Patients received treatment for up to 6 cycles. Once a patient achieved complete remission or complete remission with incomplete haematologic recovery, the Day 1 dose was reduced to 0.5mg/m^2 for the duration of the trial. **Standard-therapy:** Investigator's choice of one of the following 3 regimens: • FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor) therapy for up to four 28-day cycles (with cytarabine at a dose of 2.0g/m^2 per day on Days 1–6, fludarabine at a dose of 30mg/m^2 per day on Days 2–6, and granulocyte colony-stimulating factor at a dose of 5μg/kg per day or at the institutional standard dose) • Cytarabine plus mitoxantrone (CM) for up to four 15–20-day cycles (with cytarabine at a dose of 200mg/m^2 per day on Days 1–7 and mitoxantrone at a dose of 12mg/m^2 per day on Days 1–3; for mitoxantrone, dose reduction to 8mg was allowed based on age, coexisting conditions, and previous anthracycline use) • High dose cytarabine (HIDAC) for up to one 12-dose cycle (at a dose of 3g/m^2 every 12 hours, or a dose of 1.5g/m^2 for patients ≥55 years of age) Patients who achieved CR/CRi could undergo HSCT at the investigator's discretion. (However, some patients progressed to HSCT with CRi, and a small number of patients [8 vs 12 for inotuzumab vs SoC, respectively] received HSCT without either CR or CRi with study treatment [these patients more commonly received a new induction therapy before proceeding to HSCT]).
Permitted and disallowed concomitant	**Permitted concomitant medication:** • Any medication for a concurrent medical condition was permitted and was supplied by the study site. The use of hydroxyurea was permitted for temporary control of WBC elevations in patients with aggressive disease both prior to and during the first 5

As discussed in Section 3.1, the population in the INO-VATE 1022 trial comprised only a subset of the anticipated licenced population: "relapsed or refractory CD22-positive ALL due to receive either Salvage 1 or Salvage 2 therapy and for which either arm of randomised study therapy offered a reasonable treatment option". Therefore patients who were unable to tolerate intensive treatment were not eligible for the trial and the restriction on the number of prior salvage treatments within the trial population means that patients in the trial had a better chance of response than patients who have already received two or more salvage therapies. The ERG clinical advisor stated that the INO-VATE 1022 trial is broadly applicable to patients seen in NHS practice, although it is unclear what previous chemotherapy regimens the patients had relapsed on, and whether these previous regimens are relevant to UK practice.

Sixty-three percent of patients in the SoC arm received FLAG-based chemotherapy, 23% received CM and 14% received HIDAC. As discussed in Section 3.3, neither CM nor HIDAC are used in current NHS practice, whereas clofarabine and TKIs alone (for Ph+ patients) are used in clinical practice, but were not included as SoC in the trial.

The outcomes assessed in the trial were appropriate, although the RMST analysis was an exploratory post-hoc analysis.

The required sample size was calculated to allow adequate assessments of between group differences in remission and survival outcomes; a sample size of 218 patients was required to detect a significant difference in CR/CRi and at least 325 patients and 248 OS events were required to detect a significant difference in OS. A pre-specified analysis of CR/CRi was performed after the first 218 patients had been followed for at least three months after randomisation, with a cut-off date of 2 October 2014 (the ITT218 population). The last (326^{th}) patient was randomised to the study on 4 January 2015 and the 248^{th} OS event was reached on 8 March 2016; therefore, this date was selected as the cut-off date for OS and PFS analyses (ITT population). The safety population (also called the modified ITT (mITT) population) included all randomised patients who received at least one dose of study drug by 8 March 2016 (307 patients; 164 in the inotuzumab arm and 143 in the SoC arm). Participant baseline characteristics are summarised in Table 2, for both the ITT218 population and the full ITT population (Table 14 of the CS).

Table 2: Baseline characteristics of participants in the INO-VATE 1022 trial

	ITT218 population[a]		ITT population	
	Inotuzumab (N = 109)	**SoC (N = 109)**	**Inotuzumab (N = 164)**	**SoC (N = 162)**
Age, mean (SD)	NR	NR	45.9 (17.1)	46.0 (16.6)
Age, median (range)	47 (18.78)	47 (18–79)	46.5 (18–78)	47.5 (18–79)
Male, n (%)	61 (56)	73 (67)	91 (55.5)	102 (63.0)
Race[b], white, n (%)	76 (70)	79 (72)	112 (68.3)	120 (74.1)
ECOG PS, n (%)[c]				
• 0	43 (39)	45 (41)	62 (37.8)	61 (37.7)
• 1	50 (46)	53 (49)	81 (49.4)	80 (49.4)
• 2	15 (14)	10 (9)	21 (12.8)	20 (12.3)
• Missing data	1 (1)	1 (1)	0	1 (0.6)
Salvage-treatment phase, n (%)				
• First	73 (67)	69 (63)	111 (67.7)	104 (64.2)
• Second	35 (32)	39 (36)	51 (31.1)	57 (35.2)
• Missing data	1 (1)	1 (1)	2 (1.2)[d]	1 (0.6)[d]
Duration of first remission, n (%)				
• <12 months	62 (57)	71 (65)	98 (59.8)	108 (66.7)
• ≥12 months	47 (43)	38 (35)	66 (40.2)	54 (33.3)
Previous HSCT, n (%)	17 (16)	22 (20)	29	31
Number of previous induction therapies, n (%)				
• 1	75 (69)	69 (63)	112 (68.3)	104 (64.2)
• 2	33 (30)	39 (36)	50 (30.5)	57 (35.2)
• 3	1 (1)	1 (1)	2 (1.2)	1 (0.6)
Response to most recent previous induction therapy, n (%)				
• Complete response	78 (72)	74 (68)	121 (73.8)	111 (68.5)
• Partial response	9 (8)	7 (6)	11 (6.7)	10 (6.2)
• Treatment-resistant disease	17 (16)	18 (17)	28 (17.1)	30 (18.5)
• Progressive or stable disease	4 (4)	10 (9)	4 (2.4)	10 (6.2)

median peripheral blast count was considerably lower in the SoC arm than the inotozumab arm (30.0 versus 107.6 mm^3). The average age of patients in the trial (47 years) was lower than the average age of R/R B-cell ALL patients generally seen in NHS practice. Age has a large influence on survival outcomes in R/R B-cell ALL, therefore, survival rates may not be as high in NHS practice as in the INO-VATE 1022 trial.

2.1.1 Summary of the quality of the included trials

Results of the quality assessment of the INO-VATE 1022 trial were tabulated on page 90 of the CS. This was a large open-label trial, with appropriate methods of randomisation and allocation concealment. Treatment groups were broadly similar at baseline. The analysis included an intention-to-treat analysis, which was appropriate, and there is no evidence to suggest that the authors measured more outcomes than they reported.

Remission outcomes were assessed by an independent Endpoint Adjudication Committee (EAC) for the initial ITT218 population, but not the full ITT population; CR/CRi was assessed by the trial investigators (who were not blinded to treatment group) for the full ITT population. However, results were broadly similar between the ITT218 population and full ITT population, therefore, the ERG does not consider this to have had any significant effect on the remission outcome results.

There was an imbalance in the number of drop-outs between treatment groups, with more patients randomised to the SoC group withdrawing from the trial prior to receiving study treatment. However, the company provided baseline characteristics of the [redacted] patients who dropped out of the trial prior to receiving study treatment, as well as a summary of efficacy results for the modified ITT (mITT) population (the ITT population excluding the [redacted] patients who dropped out), which were consistent with those for the full ITT population.

2.1.2 Summary of the results of the included trials

The two primary endpoints of the INO-VATE 1022 trial were remission outcomes (the proportion of patients who achieved CR/CRi) and overall survival. Secondary endpoints included duration of remission, progression free survival, rate of subsequent HSCT and the proportion of CR/CRi patients who also achieved minimal residual disease negativity. In addition, patient-reported outcomes and adverse events were reported.

Results were presented for the full ITT population (326 patients; 08/03/16 data cutoff) for all outcomes, and for the ITT218 population (the first 218 patients; 2/10/14 data cutoff) for remission outcomes. Adverse events were reported for the 'safety population' (also called the modified ITT

Subgroup analysis results

CR/CRi rate according to baseline patient characteristics

Pre-planned subgroup analyses were performed according to baseline patient characteristics, although subgroup analyses were only presented for the ITT218 population, rather than the full ITT population. Forrest plots were presented as Figures 14 and 15 in the CS. The ERG requested clarification on why some of the numbers in Figure 14 were inconsistent with those reported in Table 14 of the CS (patient baseline characteristics), the company stated that the data in Figure 14 were based on data using the Interactive Voice Response System (IVRS), whereas data in Table 14 were from case report forms.

The only patient characteristics that did not statistically significantly favour the inotuzumab arm were the subgroup of Ph+ patients and the subgroup of t(4;11)-positive patients. However, the numbers of patients in these analyses were small, which may account for the lack of statistical significance.

Overall survival

The median overall survival (OS) was 7.7 months (95% 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. Survival probabilities were presented in Table 19 of the CS and a Kaplan-Meier plot of overall survival was presented as Figure 8. 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 boundary of P=0.0208 (2-sided alpha).

The CS stated that the OS data appeared to deviate from the proportional hazards assumption at around 15 months with the separation of curves in the Kaplan-Meier plots appearing after the median had been reached. Therefore, an exploratory post-hoc restricted mean survival time (RMST) analysis was undertaken. RMST is the mean survival time from randomisation to a clinically relevant time horizon (t*) equivalent to the area under the Kaplan-Meier curve up to the specified time. The time horizon used in the CS was the shorter of the maximum OS time in the two arms of the study, i.e. looking at the last censored event in each arm and taking the shortest, which was 24 months. In addition, a timepoint reflecting the maximum observation time from the treatment arms was also presented; 37.7 months. The ERG requested formal test evidence of non-proportionality in the overall survival data, as well as further justification for the choice of timepoint in the RMST analysis, along with analyses at earlier timepoints. In response, the company presented appropriate tests for non-proportional hazards, which were suggestive of non-proportionality, although based on only a few patients in the inotuzumab group surviving to later timepoints and the sudden drop off in the SoC group Kaplan-Meier curve at 15-20 months, based on a small number of deaths. However, the ERG accepts the company's argument for non-proportional hazards and the justification for using RMST

[redacted]

OS according to baseline patient characteristics

Pre-planned subgroup analyses were performed according to baseline patient characteristics for the full ITT population. A Forrest plot was presented as Figure 16 in the CS. The company stated that a comparison of the medians is not reflective of the whole survival distribution, due to the separation in the tails of the curves; therefore, these results should be interpreted with caution. There was no interpretation of Figure 16 presented in the CS.

The results [redacted]

Rate of subsequent HSCT

A statistically significantly higher proportion of patients in the inotuzumab group progressed to HSCT after study therapy, and prior to the start of any post induction therapy, than in the SoC group; [redacted] Details are presented in Table 5 (Table 24 in the CS).

Table 3: Subsequent HSCT in INO-VATE 1022 (ITT population)

	Inotuzumab (N = 164)	**SoC (N = 162)**
HSCT rate		
Patients with HSCT, n (%) [95% CI]	[redacted]	[redacted]
• Difference in HSCT rate between the two arms (95% CI) [p-value]	[redacted]	
Type of transplant, n (%)		
• Allogeneic	[redacted]	[redacted]
• Autologous	[redacted]	[redacted]
Type of conditioning therapy, n (%)		
• Myeloablative	[redacted]	[redacted]
• Reduced intensity	[redacted]	[redacted]

[redacted]

A further [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group had treatment delays due to adverse events. [redacted]

[redacted]

Adverse events

Adverse event data were presented for all treatment cycles and for Cycle 1 only; the average number of cycles of treatment in the inotuzumab group was 3, compared with an average of 1 cycle in the SoC group. Adverse event data for subsequent treatments received by patients were not collected (subsequent induction therapies received by patients were reported in Table 15 of the CS).

Across all cycles, [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs). During Cycle 1 [redacted] patients in the inotuzumab group and [redacted] patients in the SoC group reported treatment-emergent adverse events (TEAEs).

TEAEs by system organ class that occurred in ≥5% patients in either treatment arm were presented in Table 33 of the CS. Most TEAEs were more frequent in the SoC arm than the inotuzumab arm. However, veno-occlusive disease (VOD) was statistically significantly more frequent in the inotuzumab arm than the SoC arm [redacted]. The CS states that VOD rates were particularly high in Japanese centres, with [redacted] inotuzumab patients and [redacted] SoC patients experiencing VOD after HSCT, and describes the differences between Japanese practices and UK practice, stating that VOD rates in the UK would be expected to be lower. However, of the [redacted] inotuzumab patients who experienced VOD, [redacted], therefore, VOD cannot be dismissed due to different practices between Japanese centres and the UK. The CS also states that the rate of VOD was higher in patients who had received a prior HSCT, therefore, rates of

this study, 35 patients received inotuzumab at a dose of 1.8 mg/m^2 per cycle, of which 24 (68.6%) achieved CR/CRi and 8 proceeded to HSCT.

The MDACC observational study included 90 patients who received inotuzumab, although the first 49 patients were treated with a single-dose (1.3-1.8 mg/m^2), rather than the recommended weekly schedule (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15). This study also included some patients aged less than 18 years. In an analysis of the MDACC data including only the 75 adult patients, 41 (54.7%) achieved CR/CRi or CRp (defined as CR without platelet recovery to $\geq 100 \times 10^9$/L).

2.2 Conclusions of the clinical effectiveness section

The CS evaluation of inotuzumab was primarily based on one reasonably good quality RCT; the INO-VATE 1022 trial, which compared inotuzumab to SoC, which was the investigator's choice of FLAG, CM or HIDAC. However, the trial only included patients who were suitable for intensive therapy and were due to receive either Salvage 1 or Salvage 2 therapy, which is only a subset of the anticipated licenced population. No comparative evidence has been presented for the use of inotuzumab in patients who require third or later salvage treatment, or who are not fit for intensive treatment or may be treated with palliative intent. In addition, two of the comparator treatments in the trial (CM and HIDAC) are not used in current NHS practice, whereas two treatments that are used in NHS practice, and were specified in the NICE scope, were not used as comparators within the trial (clofarabine-based combination chemotherapy for Ph- patients and TKIs alone or in combination with clofarabine-based chemotherapy for Ph+ patients). The NICE scope also included a "best supportive care (including palliative care)" comparator, for people who are unable to tolerate chemotherapy. However, as stated previously, patients who were unfit for intensive therapy were not included in the INO-VATE 1022 trial.

The trial demonstrated that inotuzumab is effective at improving remission outcomes, with significantly more patients achieving CR/CRi than patients receiving SoC ([redacted] versus [redacted]). Inotuzumab was also associated with a statistically significantly higher proportion of patients progressing to HSCT after study therapy than SoC ([redacted]. However, [redacted] inotuzumab patients and [redacted] SoC patients received HSCT despite not achieving CR/CRi, which is not reflective of NHS practice, where patients have to have achieved CR/CRi to be eligible for HSCT. The economic model grouped all HSCT patients together, regardless of CR/CRi status. In addition [redacted] inotuzumab patients and [redacted] SoC patients who did not receive HSCT achieved CR/CRi;

Section 3.2, the ERG considers the schedule used within the INO-VATE 1022 study to be consistent with the draft marketing authorisation and importantly ensures consistency in the source of efficacy data (INO-VATE 1022) and costing assumptions applied within the model.

The comparators were based on the investigator's choice arm used in the INO-VATE 1022 trial, comprising one of the following three regimens: FLAG, CM or HIDAC. Hence, approximately [redacted] of patients were assumed to receive FLAG and [redacted] and [redacted] of patients were assumed to receive CM and HIDAC, respectively (safety population).

The company justified using the investigator's choice arm to represent the current standard of care (SoC) on the basis that while clinician feedback and literature suggest that FLAG-based combination chemotherapy regimens are established clinical practice for the majority of adults with R/R B-ALL, treatment decisions are also tailored to the individual patient. The company also considered that INO-VATE 1022 provided the most robust source to compare inotuzumab and FLAG-based regimens. As noted in Section 3.3, neither CM nor HIDAC were included in the NICE scope and the clinical advisor to the ERG did not consider that either treatment regimen reflects current NHS practice.

Within the economic model, the company included the addition of idarubicin to the FLAG regimen, since FLAG-IDA is widely administered in a UK setting. The ERG's clinical advisor confirmed that the use of FLAG-IDA would predominate in the UK. The company further assumed that the efficacy observed for FLAG in the INO-VATE 1022 trial would be equivalent to the efficacy for FLAG-IDA. This was justified on the basis of a small study (n=105) which showed no significant difference in outcomes between FLAG and FLAG-IDA.[13]

In line with final NICE scope, the company also included TKIs (in combination with the SoC chemotherapy) as a comparator in the model for Ph+ patients. However, the company stated that there is limited efficacy data concerning the effectiveness of TKIs after further lines of therapy. Consequently, while the company included the additional costs of TKI for Ph+ patients, no adjustment was applied to the efficacy estimates derived from INO-VATE 1022. The ERG considers that this approach is potentially optimistic in relation to the subsequent cost-effectiveness estimates for inotuzumab. In the absence of appropriate efficacy data from the INO-VATE 1022 trial to reflect the inclusion of TKIs assumed in the model, the ERG considers that it is more appropriate to keep the cost assumptions consistent with the efficacy data in the model.

separate survival functions specific to each state. Hence, the model structure and associated parametric survival modelling separates the patient population in INO-VATE 1022 trial into three separate sub-populations. The sub-populations and their respective sizes in the safety (modified ITT) data set are:

1. No CR/CRi & no HSCT ([redacted])
2. CR/CRi & no HSCT ([redacted])
3. HSCT & Post HSCT ([redacted])

The company stated that the model structure reflects the disease area where the main treatment goal in R/R B-cell ALL is to bridge patients to a potentially curative treatment such as HSCT and that remission is normally a pre-requisite for this. Since HSCT provides the best chance of long term survival, the company asserts that achieving CR/CRi is a key outcome and concludes that: "*the high CR/CRi rates seen within the INO-VATE 1022 trial illustrate inotuzumab's benefit patients in acting as a bridge to potentially curative therapy, so a key objective of the model was to accurately reflect this treatment benefit*" (CS, p159). Although the submission states that the model has been validated by multiple UK clinical experts as applicable to the decision problem, no details are provided in the main submission concerning the model conceptualisation process and the role of experts in validating the final model structure.

An important structural issue identified by the ERG is the absence of any explicit structural link in the proposed model between remission outcomes (CR/CRi) and HSCT. The reason for this is not made clear in the company submission but may reflect that the INO-VATE 1022 trial was open label, with no separate protocol for subsequent decisions regarding provision of HSCT. It may also reflect the decision by the company to include "*the total number of patients within the safety dataset that had an HSCT, regardless of their remission status, and regardless of their time of transplant and whether this was received prior to any post-induction therapy*" (CS, p185). The company justify this approach on the basis that it ensures "*that the economic model is reflective of what was observed within the trial, to avoid any potential misinterpretation of the outcomes*" (CS, p186). The company also consider that this approach is potentially conservative towards the benefit of inotuzumab, since a higher proportion of patients in the SoC arm received HSCT as a result of response to a subsequent induction treatment ([redacted] in the SoC arm and [redacted] in the inotuzumab arm).

The ERG has two main concerns arising from the current model structure and the use of HSCT data. Firstly, the ERG considers that the lack of an explicit link between CR/CRi and subsequent HSCT to be an important omission. Although the company employ covariate analysis within the parametric

survival modelling (see Section 5.2.6) to explore the impact of patient population characteristics (e.g. age, salvage status, prior SCT, duration of remission, Philadelphia chromosome and region), these covariates only alter the estimated survival predictions within each of the 3 main sub populations. As a result, the CR/CRi and HSCT outcomes (and hence the proportion of patients within each of the main initial health states) are derived from the overall population and are not related to specific patient characteristics and subgroups. However, since these characteristics will also potentially affect the CR/CRi and HSCT, the results of these covariate analyses were not considered by the ERG to appropriately estimate the survival of subgroups within the overall population.

Secondly, the decision to include any patient in the dataset who had an HSCT inevitably introduces additional heterogeneity. Hence, subsequent differences in survival between inotuzumab and SoC in this sub-population could be due to factors other than the treatment to which individuals were randomised. This is a particularly important aspect since the economic case being made by the company is based not only on attributing differences in the rates of CR/CRi and HSCT to inotuzumab but also to differences in the survival of patients who subsequently received HSCT.

2.2.1 Treatment effectiveness and extrapolation

The company's base case model makes use of three sets of parametric survival models (for each of the main health states/sub populations) combined with an additional assumption that individuals surviving more than three years post-HSCT would be 'cured' and return to the mortality risk for the general population.

The proportion of patients assumed to be in each of the 3 main health states from Cycle 1 was derived directly from the safety dataset from the INO-VATE 1022 trial and is reported in Table 9.

Table 4: Proportion of patient in each health state from Cycle 1

Health state	Inotuzumab	Standard of care
No CR/CRi & no HSCT	[redacted]	[redacted]
CR/CRi & no HSCT	[redacted]	[redacted]
HSCT & post-HSCT	[redacted]	[redacted]
Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant		

CS, Table 39 – p161

The use of the safety dataset (also referred to as the modified ITT dataset) excludes [redacted] of the 162 patients randomised to the investigator's choice arm. The company justified the exclusion of these

Figure 1: Kaplan-Meier data and PFS for HCST & post HSCT patients - safety population

The ERG does not consider the assumptions employed in the parametric modelling approach applied in the company base-case for the *HSCT & Post HSCT* state are robustly supported by the existing data. The ERG also has concerns regarding the clinical plausibility and external validity of the extrapolated results for this state. A recently published international reference analysis of outcomes in adults with R/R Ph-negative ALL patients [Gokbuget et al 2016] reported survival data based on 1,706 patients (including 1,416 patients with information on HSCT status). Overall survival at 36-months was reported to be 11% in the overall population (including patients who did and did not receive HSCT) and exceeded 20% in patients who received HSCT following first salvage treatment. These appear higher than the predicted survival rate of [redacted] for SoC patients in the *HSCT & Post HSCT* state within the economic model. Furthermore, the shape of the OS curve reported within the international reference analysis study for patients following receipt of HSCT after conventional chemotherapy clearly showed that the hazard of mortality was decreasing (as opposed to increasing) with time.

The uncertainties surrounding the assumptions of additional mortality benefit within the HSCT & post-HSCT state are acknowledged in the company submission and in their subsequent response to clarification questions from the ERG. Regarding the results of the additional RMST analyses provided for the HSCT & Post-HSCT state, the company states that [redacted] (Company response to ERG clarification question B6).

cure point up to 5 years and that their clinical advisors considered a range between 2 and 5 years to be clinically appropriate.

The company subsequently explored alternative cure points across the range 2 to 5 years and considered the clinical validity of subsequent predictions of post-HSCT survival based on the chosen survival distribution (Gompertz). The company noted that using later cure points (4 to 5 years) appeared to result in predictions for survival post HSCT in the SoC which were not considered clinically plausible ([redacted] of patients in the SoC were predicted to be alive at 5 years). The use of an earlier cut point at 2 years was considered too conservative to inotuzumab (with predictions of [redacted] and [redacted] of patients alive post HSCT for inotuzumab and SoC, respectively). The company concluded that the use of a 3 year cut point appeared most clinically plausible (with predictions of [redacted] and [redacted] of patients alive post HSCT for inotuzumab and SoC, respectively) and potentially conservative towards inotuzumab. Additional clinical advice received by the company supported this choice based on the visual assessments and clinical plausibility of the estimates for SoC.

The ERG considers that the choice of a specific cure point is an important source of uncertainty within the current model. The ERG is concerned that the justification for the 3 year point assumed in the base-case appears largely determined on the basis of the clinical plausibility of the survival projections based on the parametric modelling approach as opposed to reflecting the most clinically appropriate point. The ERG has previously noted potential concerns regarding the clinical validity of the parametric modelling approach applied to the *HSCT & Post HSCT* state and hence does not consider this an appropriate basis to inform the choice of cut point.

Based on a visual assessment of the overall survival curves and on post HSCT survival reported in the international reference study by Gokbuget et al (which used a sample of 1,337 patients with HSCT after 1st salvage treatment with follow up reported up to a maximum of approx. 4 years), the ERG considers that a cut point of 3 years could be potentially optimistic since a small number of further mortality events are reported beyond 36 months. However, due to the issues noted by the company and the ERG concerning the clinical validity of projections based on later cut points, the ERG advises caution in interpreting the scenario results.

A further concern relates to the structural 'cure' assumption itself and specifically the assumption that patients revert back to general population mortality rates. The ERG acknowledges that this is a common assumption applied within existing models in the general area but considers that this assumption is subject to significant uncertainty. The ERG notes that several clinical studies have