For public- AiC and CiC information redacted

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

1st Appraisal Committee meeting

Background and clinical effectiveness

Committee C

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16th May 2017

# Key clinical effectiveness discussion points

1. How will inotuzumab fit into the current treatment pathway?
   - What are the appropriate comparators? Are clofarabine and TKIs alone relevant comparators?
   - Will inotuzumab be administered 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

**Key**: ALLL, Acute lymphoblastic leukaemia; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, Haematopoietic stem cell transplant; ITT, intention to treat; RMST, Restricted mean survival time; TKI, tyrosine kinase inhibitors; SoC, standard of care.

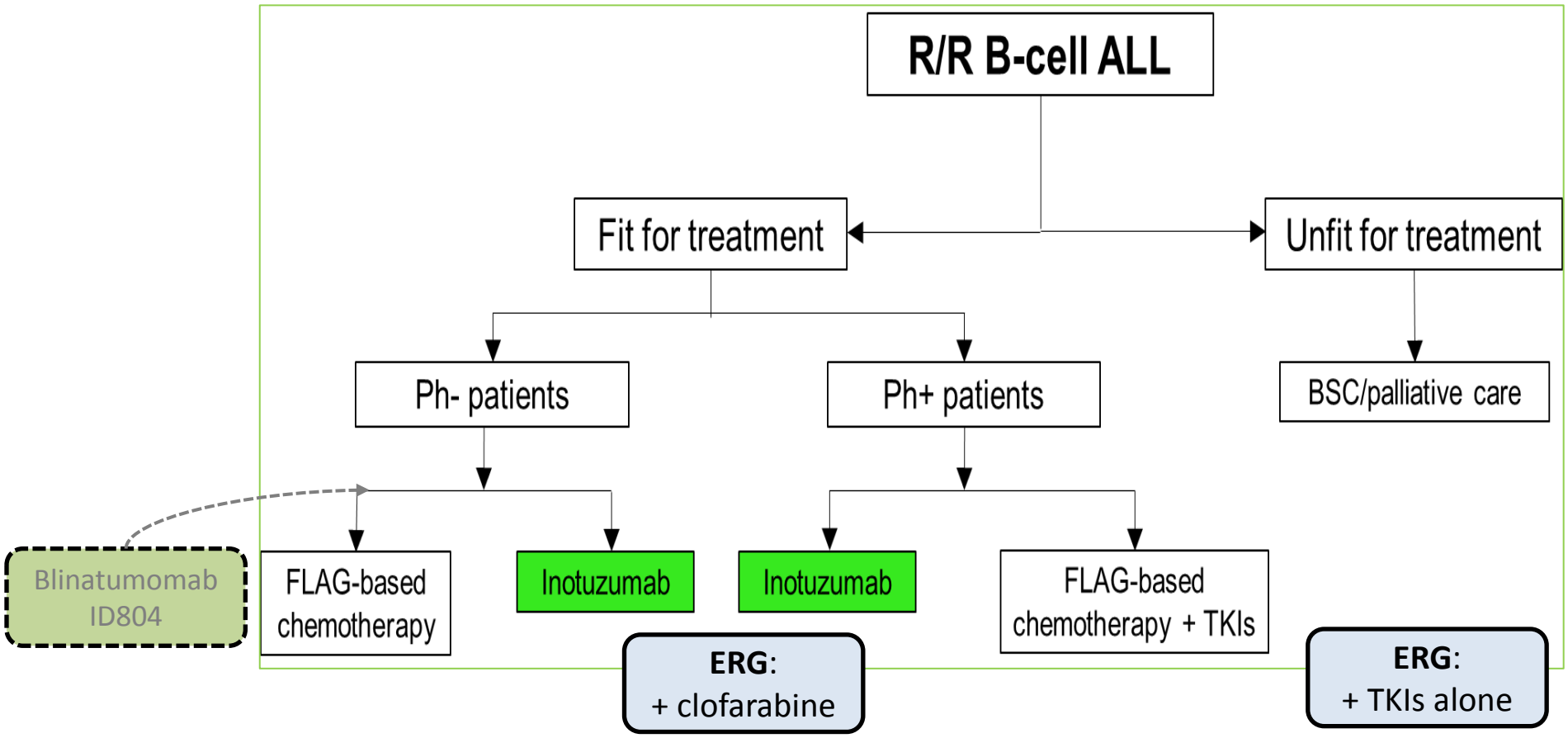
# B-cell acute lymphoblastic leukaemia

- ALL is rare in adults
- CD22 is expressed in 100% mature and 93 -96% precursor ALL[a]
- 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]
- Symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- Estimated R/R B-cell ALL population in England is 117 patients[d]
- Limited treatment options: combination chemotherapy with poor response and considerable toxicity (FLAG/FLAG-IDA and clofarabine (CDF) based regimens, and TKIs alone or in combination with chemotherapy for Philadelphia-chromosome-positive (Ph+) ALL
- The aim of chemotherapy is CR/CRi so patients can have HSCT that can potentially cure the patient

**Key:** a, b, c, d, company submission; ALL, acute lymphoblastic leukaemia; CDF, cancer drug fund; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplant; TKIs, tyrosine kinase inhibitors.

**Note:** The estimate of 117 pts is based on estimated 82% of ALL being B-cell, not 75%.

# Company 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; TKIs, tyrosine kinase inhibitors.

# Patients and carers perspective (I)
# Leukaemia CARE

- Rare and rapidly progressing disease
- Significant burden
  - *Fatigue, breathlessness, problem sleeping, nausea, vomiting, pain and memory loss*
- Treatment options are limited
  - *Most patients with relapsed or refractory ALL will be extremely ill*
  - *Older frail patients cannot tolerate aggressive therapies*
- Overall survival is often only a few months
  - *90% will die within five years*

# Patients and carers perspective (II)
# What patients want from treatments

- Improved survival
- Remission or improved response
- Improved blood count
- Reduced adverse events
- Bridge to transplant
  - *Curative option*
- Unmet need

# 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 |
| Medical form | Solution for infusion: 1-mg vial |
| Course of treatment | Over the course of treatment, it is estimated that an average of [redacted] vials will be administered. |

# 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.<br>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.<br>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). |

**Key:** BSC, best supportive care; MA, marketing authorisation.

# Decision problem (II)

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

**Key:** CM, cytarabine and mitoxantrone; BSC, best supportive care; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HIDAC, high dose cytarabine; Ph-/+, Philadelphia chromosome negative/positive; TKIs, tyrosine kinase inhibitors.

# Decision problem (III)

| | Final NICE scope | Company submission | ERG comments |
|---|---|---|---|
| Outcomes | • Overall survival<br>• Progression-free survival<br>• Treatment response rates (including haematologic responses)<br>• Time to and duration of response<br>• Adverse effects of treatment<br>• HRQL | As per scope plus:<br>• Minimal residual disease negativity (MRD-)<br>• 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 |



**Key**: HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease; QALY, quality-adjusted life year.

# 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.*
- *IO seems to 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*.

**Key**: IO, Inotuzumab ozogamicin; MRD, minimal residual disease.

# NHS England comments

- *...is confident that continued experience with the use of inotuzumab would minimise the risk of subsequent veno-occlusive disease.*
- *ALL survivors continue to be at increased risk of long term mortality*.
- *The management of patients with relapsed/refractory ALL is a specialist practice… inotuzumab to be used only in large centres which regularly assess and treat such relapsed ALL patients.*
- *There is no biologically plausible reason as to why inotuzumab would not have similar activity in children as seen in adults.*

# Trial evidence: INO-VATE1022

| | |
|---|---|
| **Design** | • Open-label, multicentre phase 3 open-label RCT |
| **Location (sites)** | 193 sites in 25 countries<br>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<br>• 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)<br>• FLAG based regimen: (63%; 102/162)<br>• Cytarabine plus mitoxantrone: (23%; 38/162)<br>• 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 |

**Key:** CR, complete remission; CRi, CR with incomplete haematologic recovery; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HIDAC, high dose cytarabine; Ph+ Philadelphia chromosome positive; TKI, tyrosine kinase inhibitor.

# 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)

| 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 | |

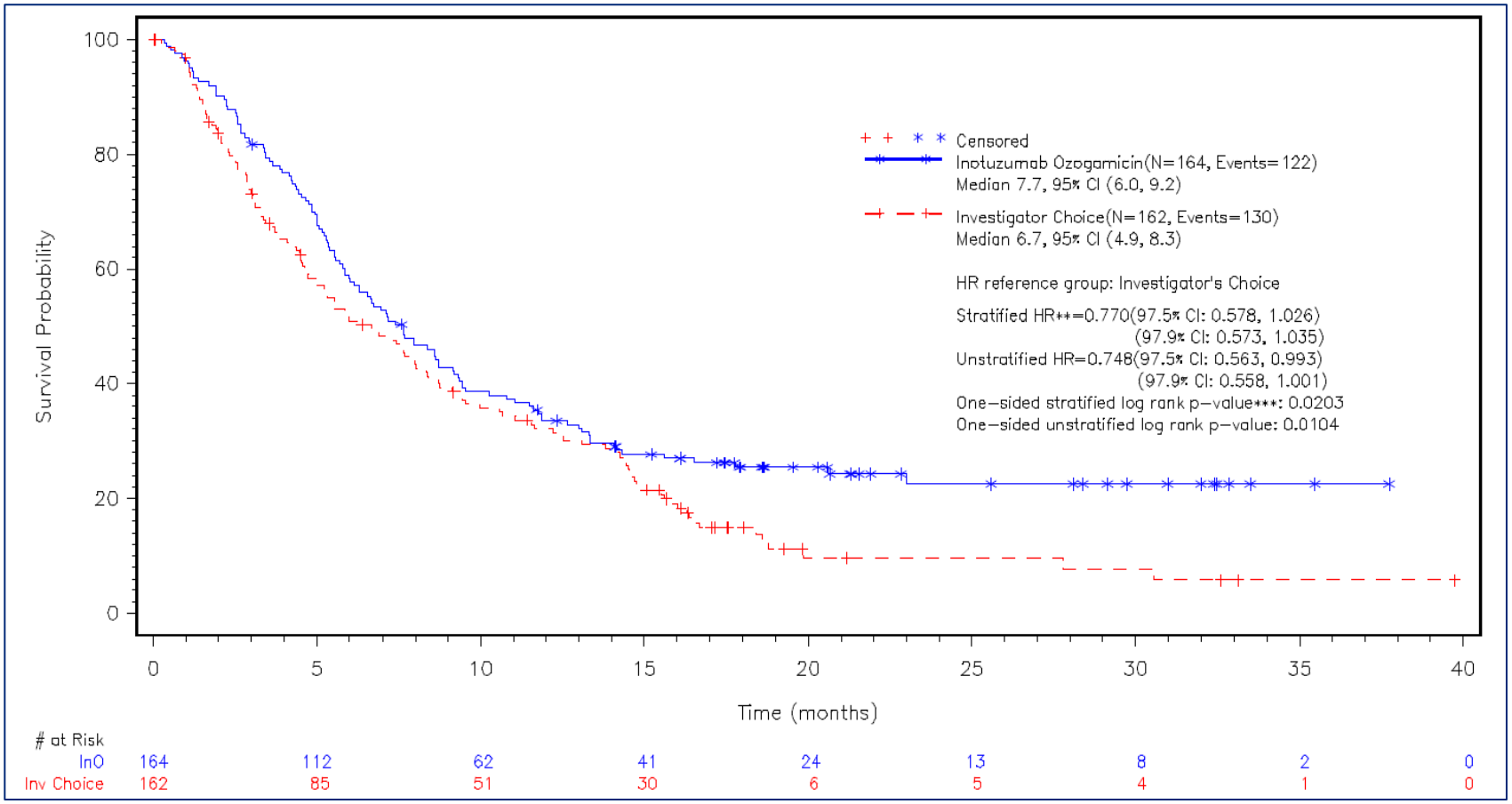
- CR/CRi assessed by an independent Endpoint Adjudication Committee for ITT218, and by the trial investigators for the full ITT population.
- results were broadly similar

**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: 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: 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)



**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.

# Key clinical effectiveness discussion points

1. How will inotuzumab fit into the current treatment pathway?
   - What are the appropriate comparators? Are clofarabine and TKIs alone relevant comparators?
   - Will inotuzumab be administered 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

**Key**: ALLL, Acute lymphoblastic leukaemia; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, Haematopoietic stem cell transplant; ITT, intention to treat; RMST, Restricted mean survival time; TKI, tyrosine kinase inhibitors; SoC, standard of care.