PART 1

For public – contains no confidential information

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease [ID6405]

This is not a highly specialised technology (HST) evaluation. This single technology appraisal (STA) is being considered by the HST committee due to scheduling and capacity

Highly specialised technologies evaluation committee [16 January 2025]

Chair: Paul Arundel

Lead team: Emtiyaz Chowdhury, Dusko Ilic, Jonathan Ives

External assessment group (EAG): Sheffield Centre for Health and Related Research (SCHARR)

Technical team: Anita Sangha, Alan Moore, Ross Dent

Company: Amgen

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease [ID6405]

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Acute lymphoblastic leukaemia (ALL)

Background: ALL is a rare type of blood cancer

- ALL causes excess production of immature lymphocyte-precursor cells (blast cells) in bone marrow
    - in adults, ~75-80% of cases arise in immature B-lymphocytes → known as B-precursor ALL
- B-precursor ALL largely characterised by expression of certain surface antigens (including CD19) and presence/absence of the Philadelphia (Ph) chromosome

Disease prognosis: ALL is rapidly progressive and usually develops over days or weeks

- 5-year survival outcomes vary by age: ~91% (<15 years), ~57% (15-39 years) and ~28% (≥40 years)*
- Current treatment aims to cure but ~45% of ALL relapses after/becomes refractory to initial treatment
- A small number of residual cancer cells may remain after achieving haematological complete remission with treatment → known as measurable/minimal residual disease (MRD)
    - prognosis is poorer with MRD-positive ALL, but risk of relapse remains with MRD-negative ALL

Epidemiology: ~765 cases of ALL in UK per year (peak age 0-4 years, ~255 cases in adults aged ≥30)

Eligible population: adults with Ph-negative, CD19-positive, B-precursor ALL with no MRD	N
NHSE estimate** (includes adults aged 30 to 70 as per inclusion criteria in key clinical trial)	47

*Estimates are for B-cell ALL from Haematological Malignancy Research Network (HMRN)
**NHS England budget impact analysis submission estimate may not differentiate by MRD status
Key sources: ID6405 final scope, company submission, Cancer Research UK

Patient perspectives

Submission from Leukaemia Care

- ALL continues to be a life-threatening illness with a high chance of relapse
  - relapsed disease is associated with significantly reduced survival and quality of life
  - older adults may be less likely to withstand multiple treatment rounds due to relapse
- Symptoms may include bone/joint pain, repeated infections, fatigue, fever and unusual bleeding/bruising
  - ALL can impact usual activities and ability to remain in work/education for both patients and carers
- ALL can also have a significant emotional impact on people with the condition, their families and carers
- Current treatment is limited and challenging due to side effects with chemotherapy
- Benefits of the technology:
  - blinatumomab may prevent relapse after initial treatment if approved for earlier use [before further disease progression]
  - survival benefit with technology would be welcomed, even if this means additional side effects to those with chemotherapy
  - may be able to be given in outpatient setting

"Given relapsed and refractory ALL continues to have poor outcomes, it is essential that clinicians have a range of frontline options suitable to the wide range of people who are affected by ALL"

Abbreviations: ALL, acute lymphoblastic leukaemia

Clinical perspectives

Submissions from 2 clinical experts

- Aim of current treatment and blinatumomab is to cure with least possible long-term side effects
- Survival outcomes with ALL remain poor, primarily due to disease relapse and toxicity from alloSCT
    - treatments which improve efficacy of front-line therapy to reduce risk of relapse are important
- Benefits of the technology:
    - blinatumomab is well tolerated compared to chemotherapy
    - trial results suggest a step change improvement in overall survival and cure rates with blinatumomab
- Other considerations:
    - additional treatment centres and training may be needed to deliver blinatumomab in this indication
    - treatment with blinatumomab may require additional MRD testing
    - MRD negative status in key clinical trial for blinatumomab was assessed by different technologies to those utilised in the UK

"Survival linked improvements in Ph-negative ALL after blinatumomab consolidation are clinically meaningful"

Abbreviations: ALL, acute lymphoblastic leukaemia; alloSCT, allogenic stem cell transplant; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Blinatumomab (Blincyto, Amgen)

<table>
<tr><td>Marketing authorisation</td><td>

Blinatumomab is indicated for the treatment of adults with Ph-negative, CD19-positive, B-precursor ALL in the consolidation phase (license extension)
MHRA license extension issued on 16 December 2024 (orphan drug designation)
Approved for other indications in B-precursor ALL

</td></tr>
<tr><td>Mechanism of action</td><td>Monoclonal antibody → binds specifically to CD19 expressed on the surface of B-cell ALL blasts while simultaneously binding to CD3 on the surface of T-cells</td></tr>
<tr><td>Administration</td><td>

Blinatumomab is administered by continuous intravenous infusion using an infusion pump over a period of up to 96 hours. Recommended dosage in this indication:
<table>
<tr><th>Consolidation cycles</th><th>Weight ≥45 kg</th><th>Weight <45 kg</th></tr>
<tr><td>Days 1–28</td><td>28 mcg daily</td><td>15 mcg/m^2 daily*</td></tr>
<tr><td>Days 29–42</td><td>14-day treatment-free interval</td><td>14-day treatment-free interval</td></tr>
</table>

Philadelphia chromosome and MRD testing are necessary to determine eligibility for blinatumomab use → used routinely in clinical practice for B-precursor ALL

</td></tr>
<tr><td>Price</td><td>

List price is £2,017 for a 38.5 mcg vial
Average cost of blinatumomab per cycle is £56,476 (based on 28 vials at list price)
Company has a confidential commercial arrangement [simple discount patient access scheme (PAS)]

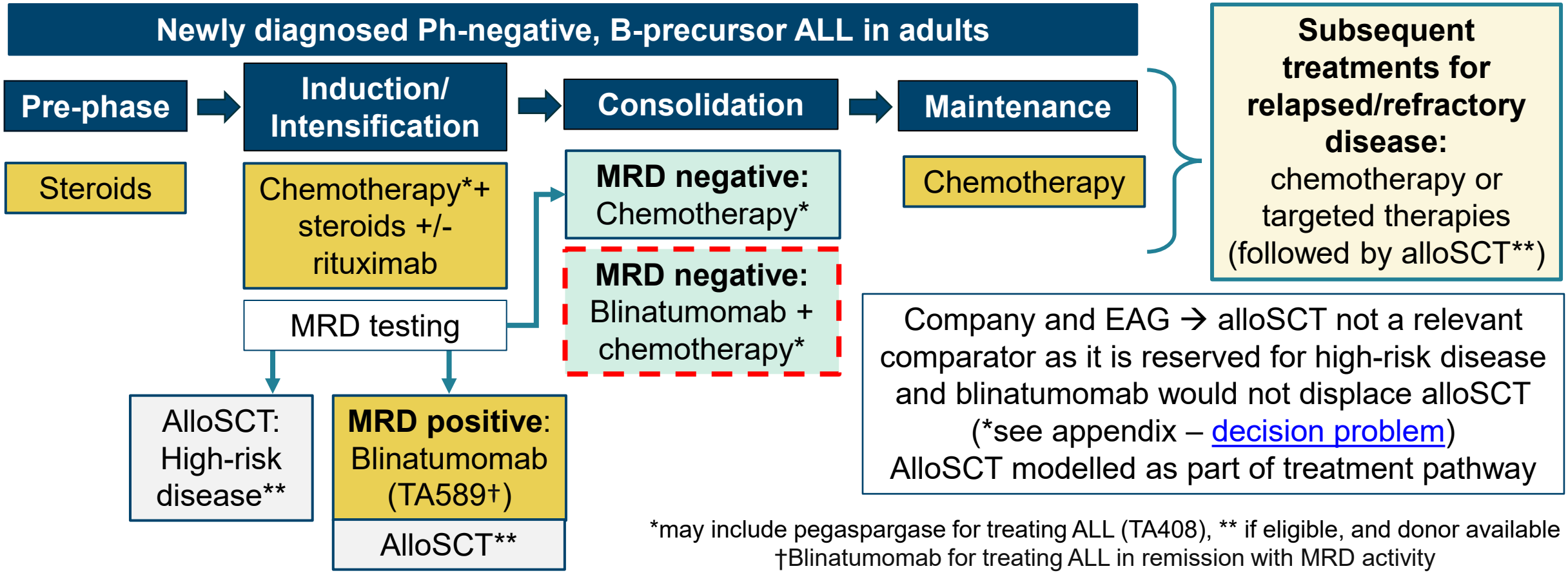
</td></tr>
</table>

*dose should not exceed 28 mcg daily

Abbreviations: ALL, acute lymphoblastic leukaemia; mcg, micrograms; MHRA, Medicines & Healthcare Products Regulatory Agency; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Treatment pathway for Ph-negative, B-precursor ALL

Pathway based on UKALL14 protocol → typically used in NHS clinical practice for adults with B-precursor ALL (usually aged 25-65, *see appendix – UKALL14)



*may include pegaspargase for treating ALL (TA408), ** if eligible, and donor available
†Blinatumomab for treating ALL in remission with MRD activity

Company's positioning of blinatumomab (with chemotherapy): adults with Ph-negative, CD19-positive, B-precursor ALL that is MRD-negative at the start of the consolidation phase (narrower than MA wording → does not restrict blinatumomab use by MRD status or to the start of consolidation therapy)

Abbreviations: ALL, acute lymphoblastic leukaemia; alloSCT, allogenic stem cell transplant; MA, marketing authorisation; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Key issues

Issue	ICER impact
Exclusion of adults aged <30 years from E1910 trial	Unknown
Differences in measurable/minimal residual disease thresholds	Unknown
Uncertainty around long-term overall survival and relapse-free survival	Small to moderate

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Key clinical trial – E1910

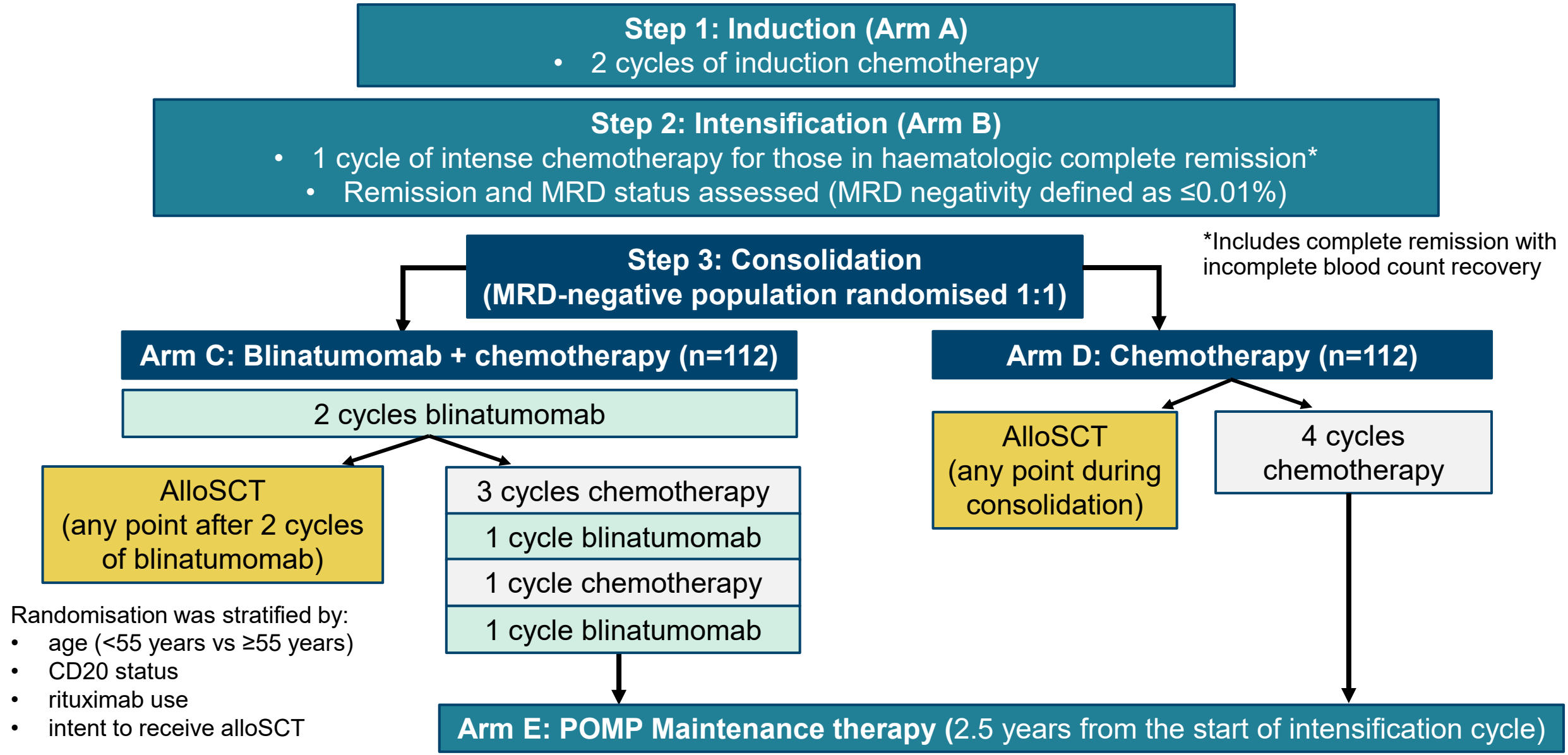
	E1910 [Ongoing → 10-year follow-up from the start of induction treatment]
Design + location	Phase 3, randomised, open-label trial. 77 centres in the US, Canada and Israel
Population	Adults aged between 30 and 70 with newly diagnosed Ph-negative, B-precursor ALL* (only MRD-negative population is relevant to this appraisal – see bullet point 1 in box)
Intervention (n=112)	Blinatumomab (4 cycles, each cycle = 28 mcg daily over 28 days + 14 days rest) plus standard of care consolidation chemotherapy (4 cycles, treatments detailed below)
Comparator (n=112)	Standard of care consolidation chemotherapy alone (4 cycles): • Cycles 1, 2 and 4 (28 days): cytarabine, etoposide, methotrexate, rituximab (if CD20+), pegaspargase (≥55 years, cycle 1 only) • Cycle 3: (42 days): daunorubicin, vincristine, dexamethasone, methotrexate, cyclophosphamide, cytarabine, 6-mercaptopurine, rituximab (if CD20+)
Primary outcome	Overall survival (OS)
Secondary outcomes	Key outcomes: relapse-free survival (RFS), adverse events (AEs)

- Trial initially included participants with MRD-positive disease (MRD status was a stratification factor)
  - protocol was amended (2018) due to FDA accelerated approval of blinatumomab in people with MRD-positive ALL → this population was no longer randomised and instead assigned to intervention arm
- Company and EAG clinical experts → chemotherapy regimen in E1910 is very similar to UKALL14 protocol

*CD19-positivity was not mandated for eligibility given its high incidence at B-cell ALL diagnosis

Abbreviations: ALL, acute lymphoblastic leukaemia; FDA, U.S Food and Drug Administration; mcg, microgram; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

E1910 trial design

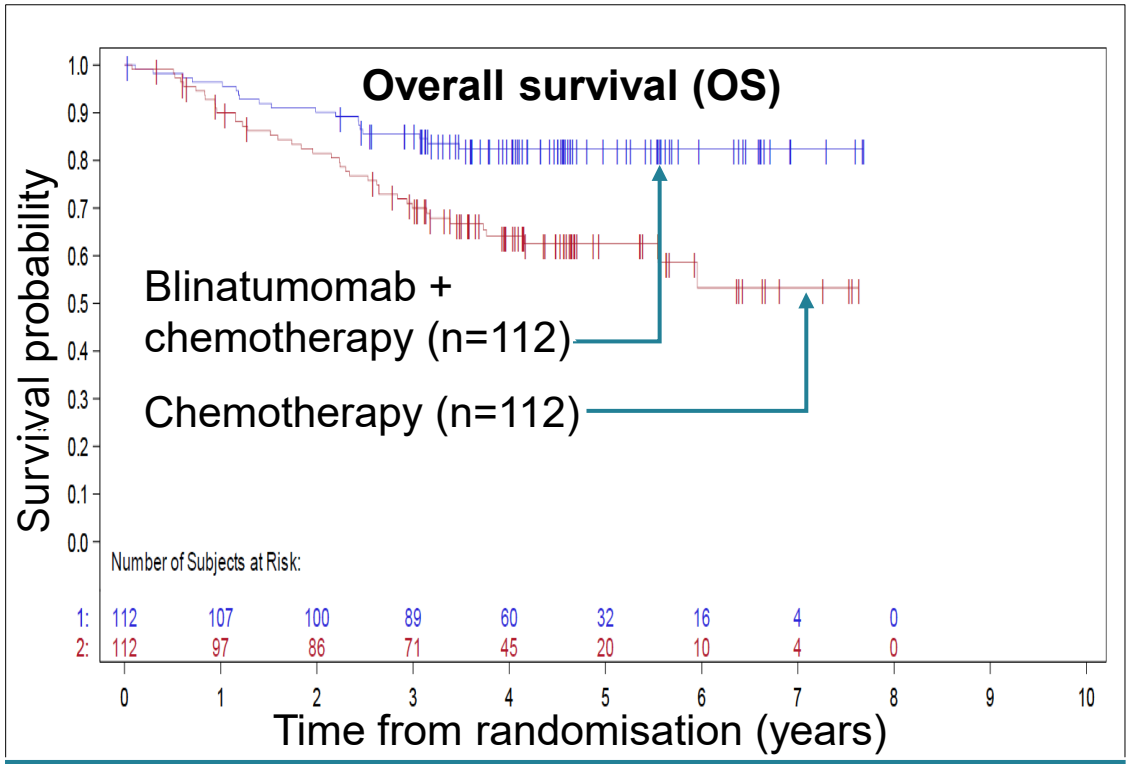


Randomisation was stratified by:
- age (<55 years vs ≥55 years)
- CD20 status
- rituximab use
- intent to receive alloSCT

Abbreviations: alloSCT, allogenic stem cell transplant; MRD, measurable/minimal residual disease; POMP: vincristine, prednisolone, methotrexate, 6-mercaptopurine

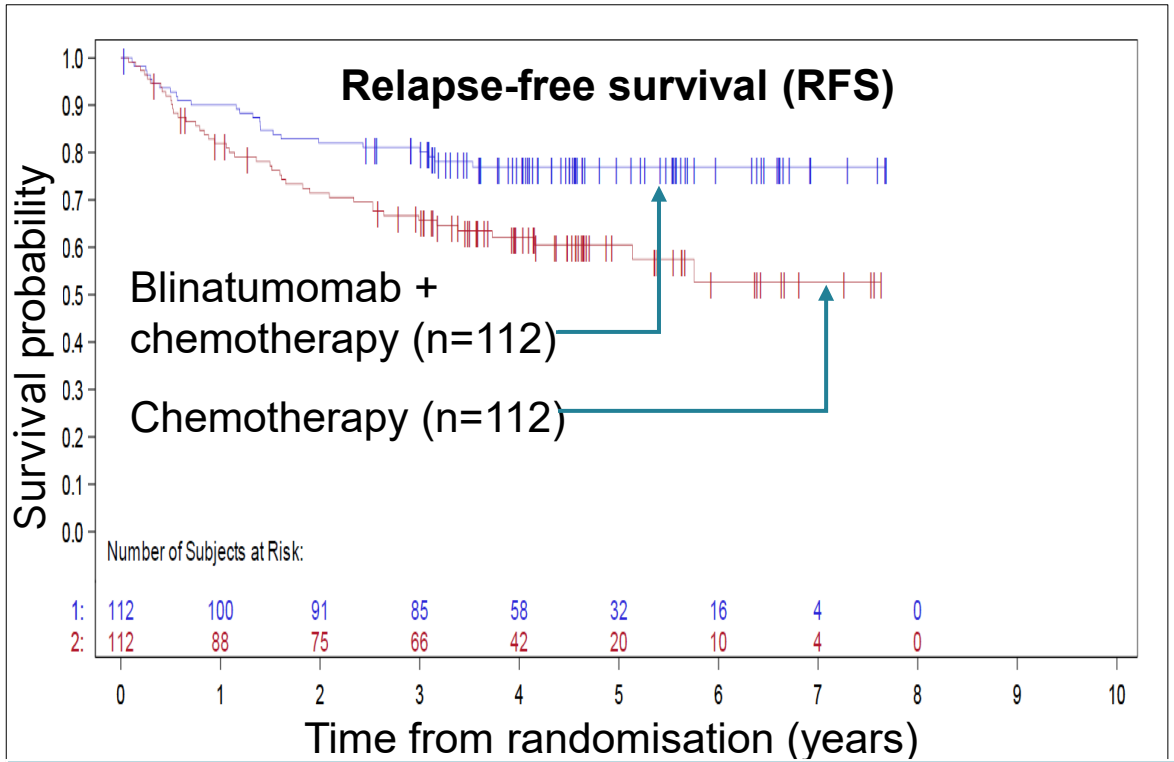
E1910 results – Overall survival and relapse-free survival

Results from full analysis set, MRD-negative population, primary analysis data cut-off June 2023
(median follow-up time = 4.5 years both arms)



OS HR blinatumomab + chemotherapy vs chemotherapy

0.44 (95% CI 0.25 to 0.76), p-value = 0.001



RFS HR blinatumomab + chemotherapy vs chemotherapy

0.53 (95% CI 0.32 to 0.88), p-value = 0.006

Median overall survival and relapse-free survival were not reached in either arm

Abbreviations: CI, confidence interval; HR, hazard ratio; MRD, measurable/minimal residual disease

NICE

Unknown impact on ICER

Key issues: Exclusion of adults aged <30 from E1910

Background

- Chemotherapy regimen in E1910 largely reflects UKALL14 protocol (typically used for adults aged 25-65)
- Inclusion criteria in E1910 trial included adults aged 30-70 years (mean age at enrolment = 50.1 years)
- Licensed population includes all adults (no age cut-off) → but clinical and cost effectiveness in relevant population aged under 30 years is unknown

EAG clinical expert comments

- Lower age cut-off of 30 years in trial was because of practical considerations (relating to health care insurance system in US) rather than any underlying biological rationale
- Blinatumomab is expected to be effective in adults who are under 30 years of age:
  - a positive NICE recommendation for blinatumomab restricted by an age cut-off of 30 years would lead to inequality of access for younger adults with ALL [such as those whose ALL is managed under UKALL14 protocol but are younger than the age cut-off in E1910 trial (people aged >25 and <30)]

Equality considerations: stakeholder comments

- Trial applies an upper age limit → standard approach is to individualise treatment decisions on biologic, personal and clinical parameters. This evaluation should reflect clinical practice and not necessarily restrict to a clinical trial defined criteria when determining benefit

Is the chemotherapy regimen for younger adults (<25 years) similar to the UKALL14 protocol?
Are the trial results generalisable to adults of all ages who would be eligible for blinatumomab?
Are there any equality issues that need to be considered?

Abbreviations: ALL, acute lymphoblastic leukaemia

Unknown impact on ICER

Key issues: Differences in MRD thresholds (1)

Background – measurable/minimal residual disease (MRD)

- MRD tests investigate the presence of detectable cancer cells in the bone marrow or blood at a level above (MRD-positive) or below (MRD-negative) a certain threshold when disease is in remission
- MRD thresholds considered in appraisals of blinatumomab for Ph-negative, B-precursor ALL

NICE TA589* (Key trial = BLAST)	ID6405 (Key trial = E1910)
MRD threshold = 0.1%	MRD threshold = 0.01%

- In TA589, blinatumomab was deemed to be cost-effective in MRD-positive population (0.1% threshold)

EAG comments (1)

- EAG clinical experts commented:
  - MRD threshold used in E1910 trial is reasonable and any positive MRD measurement (detectable disease at any threshold) should be classed as MRD-positive disease
  - A positive recommendation for blinatumomab based on the MRD threshold applied in E1910 would leave some people with MRD-positive disease ineligible for treatment because although they have detectable MRD, it has not yet reached the threshold specified for treatment in TA589
    - ➢ this would disadvantage people with an MRD of between 0.01% and 0.1%
    - ➢ if this happens → MRD must be monitored until progression (high-risk as relapse rarely linear)

*NICE TA589 = Blinatumomab for treating acute lymphoblastic leukaemia in remission with MRD activity

Abbreviations: ALL, acute lymphoblastic leukaemia; Ph, Philadelphia chromosome

Unknown impact on ICER

Key issues: Differences in MRD thresholds (2)

EAG comments (2)

- EAG considers any positive recommendation for blinatumomab in the MRD-negative ALL population should be carefully phrased so people are not left ineligible for treatment with no biological basis for their exclusion

Equality considerations: stakeholder and clinical expert comments

- Population who have MRD-positive disease (>0.01% but <0.1%) have a high risk of relapse but will not be eligible for blinatumomab based on current (NICE TA589) and proposed (ID6405) MRD thresholds
  - population has been orphaned not for clinical or biological rationale but because of trial designs
- Older people and certain biological subgroups may not have equal access to standard MRD monitoring due to lack of an identifiable MRD marker
  - alternative MRD assessment approaches ensure equitable access to MRD indicated therapy
- Small proportion of people may not be evaluable for MRD testing (such as sample failure or lack of an applicable molecular/flow based MRD assay)
  - subgroup should not be discriminated against based on technical factors related to MRD testing

The initial marketing authorisation for MRD-positive disease specified a 0.1% threshold so the TA589 recommendation needed to follow this. The license extension does not specify MRD status, so for this guidance on MRD-negative disease, the committee does not have to specify a threshold but may consider it necessary to include the trial definition of 0.01% to reflect the evidence base. If it is necessary, are there any equality issues that need to be considered?

Abbreviations: ALL, acute lymphoblastic leukaemia; MRD, measurable/minimal residual disease

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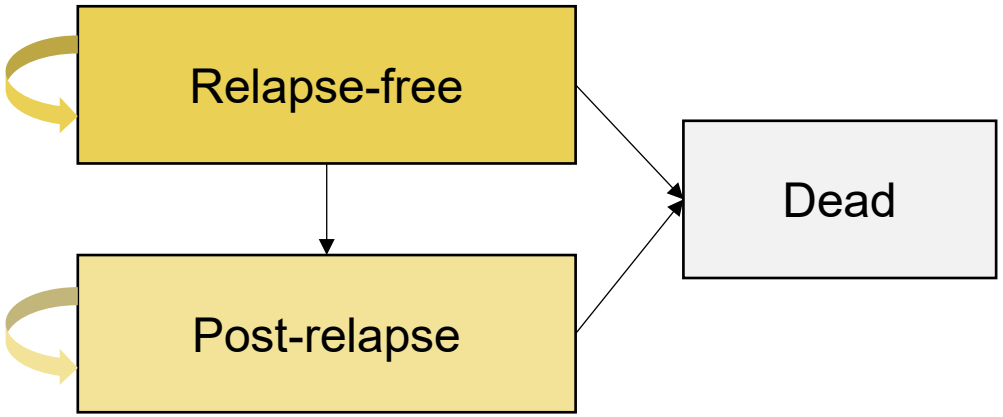
Company's model overview (1)



Population modelled: adults with CD19-positive, Ph-negative, B-precursor ALL that is MRD-negative at the start of the consolidation phase
Baseline characteristics: E1910 trial
Age at model entry: 50.1 years

Partitioned survival model (area under the curve model)

- 3 mutually exclusive health states: relapse-free, post-relapse and dead
- Cycle length: 1 week with no half-cycle correction. Time horizon: 50 years (lifetime)
- People enter model in the relapse-free health state and receive either blinatumomab + consolidation chemotherapy or consolidation chemotherapy alone (in line with E1910 trial)
  - those who remain relapse-free have maintenance therapy for up to 2.5 years
    - maintenance therapy = POMP (6-mercaptopurine, methotrexate, vincristine, prednisolone)
  - those who relapse after consolidation or maintenance receive subsequent treatment (first 5 years of model time horizon only)

Relapse defined as: presence of blasts in the blood or >5% blasts in bone marrow not attributable to another cause (as per E1910 trial)
Abbreviations: ALL, acute lymphoblastic leukaemia; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Company's model overview (2)

- AlloSCT is not included as a comparator but modelled as part of treatment pathway (before/after relapse)
  - modelled RFS and OS probabilities are structurally unrelated to the receipt of alloSCT
  - proportion who received alloSCT (before relapse) was low and comparable between arms in E1910
- Model assumes that people whose disease remains relapse-free after 5 years is cured (per clinical opinion)
- 5-year cure time point acts as a cap on costs and QALYs:
  - utilities for people in relapse-free state rebound to age-and-sex matched general population norms
  - no ALL-related costs are incurred after this time point (subsequent therapy, alloSCT and terminal care)
  - QALY losses with post-relapse alloSCT and terminal care are not applied

Proportion receiving alloSCT in model (based on MRD-negative population in E1910 trial)

Health state	Blinatumomab + chemotherapy	Chemotherapy
Relapse-free	[redacted]	[redacted]
Post-relapse* (occurring in first 5 years)	[redacted]	[redacted]

EAG considers the model structure appropriate for addressing the decision problem

*Proportions receiving alloSCT post-relapse are only applied to people whose disease relapses (not to all people who start treatment)

Abbreviations: ALL, acute lymphoblastic leukaemia; alloSCT, allogenic stem cell transplant; MRD, measurable/minimal residual disease; OS, overall survival; QALY, quality-adjusted life year; RFS, relapse-free survival;

Utility values

Utility values for health states used in the model

- No HRQoL data collected in E1910 trial → utilities align with those used in NICE TA589
- BLAST trial (blinatumomab for Ph-negative, MRD-positive B-precursor ALL in complete remission) informs:
  - relapse-free utility: EQ-5D data taken from MRD-responders (people whose disease changed from MRD-positive to MRD-negative)
- TOWER trial (blinatumomab vs chemotherapy for relapsed/refractory Ph-negative B-precursor ALL) informs:
  - post-relapse utility: EQ-5D data from those receiving standard of care salvage chemotherapy with matching between participants in TOWER and BLAST

Health state	Utility value	
	Blinatumomab + chemotherapy	**Chemotherapy**
Relapse-free	• On-treatment*: 0.840 • Off-treatment: 0.850	0.850
Post-relapse	0.692	
Death	-0.129**	

EAG comments

- Utilities are adjusted for increasing age
- Post-relapse utility is implausibly high
- Exploratory scenarios presented by company and EAG using lower post-relapse utilities → result in small reductions in the ICER

*Utility decrement applied for disutility associated with continuous IV infusion

** Terminal care disutility (informed by BLAST trial, applied to people who die within 5 years of model entry)

Abbreviations: ALL, acute lymphoblastic leukaemia; EQ-5D, EuroQol- 5 Dimension; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Other key inputs and assumptions

Intervention and comparator efficacy	• Mixture-cure models fitted to OS and RFS data from E1910
	  ○ cured fraction: assumes age-and-sex matched general population mortality
	  ○ non-cured fraction: follows standard parametric survival trajectory
	  ○ standardised mortality ratio applied to general population mortality for any residual complications (to both cured + non-cured populations)

AlloSCT	Disutility related to alloSCT (applied up to the cure time point of 5 years)
Adverse events (AEs, first model cycle only)	• Costs and disutilities applied for grade ≥3 TEAEs from consolidation phase of E1910 (≥5% occurrence in either arm) and grade ≥3 CRS in blinatumomab arm • AEs related to subsequent drug treatments are not included
Other costs (first 5 years only)	Costs associated with consolidation therapy, maintenance therapy, alloSCT, subsequent treatments and terminal care are included
Subsequent treatments* (upon relapse)	• 1 subsequent line of drug-treatment only. Proportions based on clinical opinion and differ by arm: blinatumomab, inotuzumab ozogamicin and FLAG-IDA • AlloSCT (in addition to subsequent drug treatment)
Drug wastage	Included for all drugs administered intravenously

*Model excludes brexucabtagene autoleucel (as recommended for use within the Cancer Drugs Fund in NICE TA893) and tisagenlecleucel (as recommended only for people aged ≤25 in NICE TA975)

Abbreviations: alloSCT, allogenic stem cell transplant; CRS, cytokine release syndrome; FLAG-IDA, fludarabine, cytarabine, filgrastim and idarubicin; OS, overall survival; RFS, relapse-free survival; TEAE, treatment-emergent adverse event

Small to moderate impact on ICER

Key Issue: Uncertainty around long-term OS and RFS (1)

Background – choice of mixture-cure model (MCM)

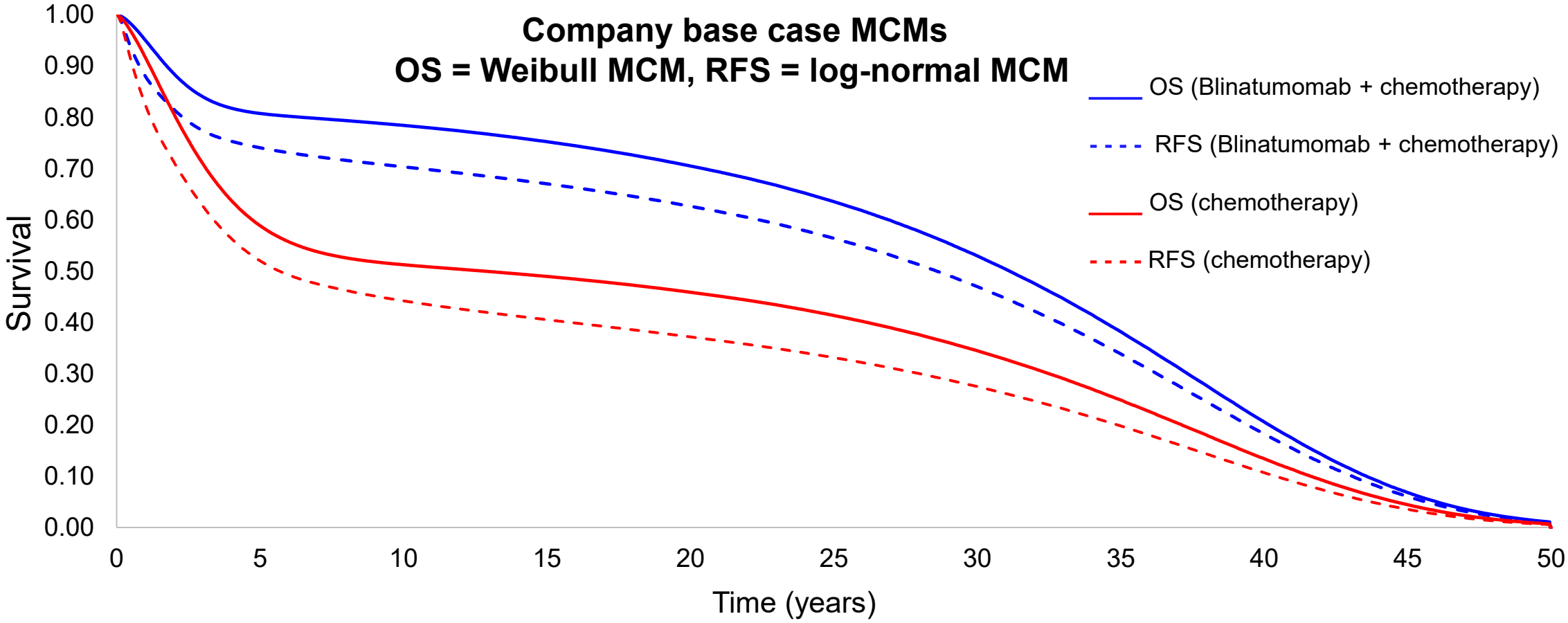
- OS and RFS were estimated separately for both arms using individual patient data from E1910
- For OS, company base case → Weibull MCM selected for both arms (*see appendix – slides 39 to 41)
- For RFS, company base case → log-normal MCM selected for both arms (*see appendix – slides 42 to 44)

EAG comments

- Long-term OS and RFS projections uncertain due to limited sample size and short follow-up in E1910
- Company's survival analysis methods are appropriate → EAG base case retains same models
- EAG explored further scenarios:
  - selecting all other clinically plausible alternative MCMs for OS and RFS → minimal impact on ICER
  - RFS and OS follow Kaplan-Meier estimates from E1910 followed by fixed cure point at 5 years and 7.5 years (hazards switch to those estimated from SMR-uplifted age-and sex-matched general population life tables) → small to moderate impact on ICER, but EAG does not prefer these analyses over use of MCMs in this case

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; RFS, relapse-free survival; SMR, standardised mortality ratio

Key Issue: Uncertainty around long-term OS and RFS (2)



RFS and OS include uplifted mortality risks using an SMR of 1.09 for cured and uncured populations

Are the company's survival analyses appropriate for decision-making?

Abbreviations: MCM, mixture-cure model; OS, overall survival; RFS, relapse-free survival; SMR, standardised mortality ratio

Small to moderate impact on ICER

Key Issue: Uncertainty around long-term OS and RFS (3)

Background – standardised mortality ratio (SMR)

- SMR of 1.09 was applied to cured and non-cured parts of MCMs for RFS and OS in company base case
  - company note SMR of 1.09 has been used in previous NICE appraisals for large B-cell lymphoma
- Company clinical experts considered that SMRs of 3.0 and 4.0 used in previous NICE appraisals for B-cell ALL were too high for target population:
  - SMR of 4.00 used in NICE TA589 is based on a study evaluating survival post-transplant → most people in E1910 trial did not receive a transplant (before relapse)
  - SMR of 3.0 used in NICE TA893* is based on a trial in the relapse/refractory setting → E1910 trial included people with MRD-negative disease in the frontline consolidation setting
- Company clinical experts indicated that an SMR of 1.09 would be plausible for appraisal population

EAG comments

- Uncertainty around magnitude of SMR applied but EAG clinical experts supported use of a low SMR in the MRD-negative population as they are unlikely to undergo alloSCT → EAG base case retains same SMR
- EAG explored further scenarios:
  - applying higher SMRs (2.0 and 3.0) → small to moderate impact on ICER, but EAG considers these are likely to be overestimates for target population

Is an SMR of 1.09 appropriate for the target population?

*Brexucabtagene autoleucel for treating relapsed or refractory B-cell ALL in people 26 years and over

Abbreviations: ALL, acute lymphoblastic leukaemia; ICER, incremental cost-effectiveness ratio; MCM, mixture-cure model; MRD, measurable/minimal residual disease; OS, overall survival; RFS, relapse-free survival

EAG preferred amendments to model

1) Correction of remaining model errors and other minor issues

- Use of life tables for England, correction of drug pack sizes/costs, inclusion of half-cycle correction
- General population utility multiplier removed when the age-and sex-matched general population utility value is applied to people whose disease is relapse-free (those not reflected by the cure fraction) after 5 years

2) Adjustment of RFS to account for proportion of RFS events which are deaths

- Costs and QALY losses with subsequent treatments and alloSCT are applied only to non-fatal events

3) Inclusion of health care resource use (HCRU*) costs with no 5-year cap for post-relapse state

- Inclusion of HCRU costs associated with clinic visits and monitoring after consolidation therapy for people in relapse-free and post-relapse health states (implemented using additional functionality in company model)
- Amended model to remove 5-year cap on HCRU costs for people in post-relapse health state

4) Removal of 5-year cap for subsequent treatment/alloSCT costs and QALY losses

- Inclusion of costs of subsequent treatments (drug treatments and alloSCT) and disutility with alloSCT post-relapse regardless of when cure is expected (as model predicts that some relapses occur after 5 years)

EAG amendments have a minimal impact on the ICER

*HCRU costs do not include ongoing costs related to MRD testing

Abbreviations: alloSCT, allogenic stem cell transplant; QALY, quality-adjusted life year; RFS, relapse-free survival

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Correction of model errors and minor issues identified by EAG	Not included	Included
Distribution used to model OS for both arms	Weibull MCM	Weibull MCM
Distribution used to model RFS for both arms	Log-normal MCM	Log-normal MCM
Adjustment of RFS for fatal events	Not included	Included
HCRU costs for clinic visits and monitoring	Not included	• Included for relapse-free and post-relapse health states • Removal of 5-year cap in post-relapse health state
5-year cap for costs of subsequent treatment/alloSCT and QALY losses	Included	Not included

Abbreviations: alloSCT, allogenic stem cell transplant; HCRU, health care resource use; MCM, mixture-cure model; OS, overall survival; QALY, quality-adjusted life year; RFS, relapse-free survival

Cost-effectiveness results

As confidential discounts are available for treatments in the pathway, ICERs will be presented in Part 2 slides

ICER ranges have been presented below to aid transparency

Summary – blinatumomab + chemotherapy versus chemotherapy alone

- Company and EAG agree that no additional QALY weighting for severity should be applied
  - company base case probabilistic ICER: above £30,000/QALY gained
  - EAG preferred analysis probabilistic ICER: above £30,000/QALY gained

Summary of EAG scenarios presented in part 2:	ICER impact
1) RFS and OS based on KM function with cure time point at 5 years and 7.5 years 2) SMR of 2.0 and 3.0	Scenarios 1-2: Small to moderate
3) Selecting all other clinically plausible alternative MCMs for OS and RFS 4) Post-relapse utility of 0.50 and 0.25 5) Inclusion of subsequent treatment adverse event costs and disutilities 6) Pre-relapse alloSCT proportion = 0% 7) Adjustment for fatal RFS events excluded 8) HCRU costs applied from start of consolidation (rather than after consolidation) 9) Relapse-free utility applied indefinitely (no rebound to general population utility)	Scenarios 3-9: Small

Abbreviations: alloSCT, allogenic stem cell transplant; HCRU, health care resource use; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; QALY, quality-adjusted life year; RFS, relapse-free survival; SMR, standardised mortality ratio

Other considerations

Innovation

- Company highlight that blinatumomab is the first targeted therapy to be approved for Ph-negative, B-precursor ALL that is MRD-negative and in the frontline consolidation phase

Benefits not captured in the QALY calculation

- Company highlight that uncaptured benefits in the cost-effectiveness analysis include:
  - wider indirect benefits of blinatumomab plus chemotherapy to people with ALL, their carers and society
  - sense of hope that blinatumomab plus chemotherapy may offer to people with ALL and their families

Abbreviations: ALL, acute lymphoblastic leukaemia; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome; QALY, quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company submission does not include a managed access proposal for blinatumomab

- E1910 trial is ongoing with 10 years follow-up post induction treatment
  - final analysis results (next data-cut) expected in [redacted]
- Golden Gate trial [Phase 3, RCT assessing blinatumomab alternating with low-intensity chemotherapy versus standard of care chemotherapy for older adults (aged ≥55 years) with Ph-negative B-precursor ALL]
  - primary analysis results expected [redacted]

Abbreviations: ALL, acute lymphoblastic leukaemia; Ph, Philadelphia chromosome; RCT, randomised controlled trial

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease [ID6405]

- Background and key issues
- Clinical effectiveness
- Modelling and cost effectiveness
- **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issue	ICER impact	Slide
Exclusion of adults aged <30 years from E1910 trial	Unknown	13
Differences in measurable/minimal residual disease thresholds	Unknown	14
Uncertainty around long-term overall survival and relapse-free survival	Small to moderate	21

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease [ID6405]

Supplementary appendix

NICE National Institute for Health and Care Excellence

UKALL14 protocol (1)

Link back to treatment pathway slide

- **UKALL14 was a phase 3, randomised controlled trial which included a comparison of rituximab + standard chemotherapy vs standard chemotherapy in adults with newly diagnosed B-precursor ALL**
  - participants (n=586) were randomised between 2012 and 2017 across 65 NHS ALL centres
  - included adults aged between 25-65 years
  - rituximab was given as 4 doses during the induction phase of the trial to those randomised to the rituximab arm (see next slide for summary of trial phases and treatments)
  - addition of rituximab did not significantly improve event-free survival vs standard chemotherapy
- **In the UK, newly diagnosed Ph-negative, B-precursor ALL in adults aged between 25 and 65 is usually treated according to the standard chemotherapy arm of the UKALL14 protocol:**
  - people whose disease is high-risk or MRD positive after induction/intensification therapy may receive alloSCT (and so would not have consolidation or maintenance treatment)
  - in older people, disease may be treated according to the UKALL60+ protocol if they are unsuitable/unfit to follow the UKALL14 protocol

Abbreviations: ALL, acute lymphoblastic leukaemia; alloSCT, allogenic stem cell transplant; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

UKALL14 protocol (2)

Link back to treatment pathway slide

Summary of treatments in UKALL14 trial for Ph-negative, B-precursor ALL

Treatment phase	Treatments
Steroid pre-phase (5-7 days): aims to reduce blast count and risk of complications	• Dexamethasone
Induction (2 cycles over 8 weeks): aims to induce complete remission	• Cycle 1: daunorubicin, vincristine, dexamethasone, peg-asparaginase, methotrexate and rituximab (if randomised to rituximab arm only) • Cycle 2: cyclophosphamide, cytarabine, mercaptopurine, methotrexate
Intensification (1 cycle over 4 weeks): aims to reduce risk of CNS relapse	• Cycle 1: methotrexate, peg-asparaginase
Consolidation (4 cycles): aims to consolidate initial response and eradicate any remaining cancer cells	• Cycle 1: cytarabine, etoposide, peg-asparaginase, methotrexate • Cycles 2 & 4: cytarabine, etoposide, methotrexate • Cycle 3: daunorubicin, vincristine, peg-asparaginase, dexamethasone, methotrexate, cyclophosphamide, cytarabine, mercaptopurine
Maintenance (2 years): aims to maintain remission and prevent cancer regrowth	• Vincristine, prednisolone, mercaptopurine, methotrexate

Abbreviations: ALL; acute lymphoblastic leukaemia; Ph, Philadelphia chromosome

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with Ph-negative CD19-positive MRD-negative B-precursor ALL in frontline consolidation	Narrower than scope as focuses on adults only. This is in line with the clinical evidence for blinatumomab in this indication and with the anticipated positioning of blinatumomab in clinical practice	• Population is consistent with evidence from E1910 trial • MRD-negative population would be covered by the anticipated extension to the MA for blinatumomab • E1910 enrolled adults aged 30-70 years. EAG's clinical advisors expect blinatumomab to also be effective in younger adults aged <30 years • Study E1910 defined MRD status based on a threshold of 0.01%
Intervention	Blinatumomab with chemotherapy	In line with final scope	In line with final scope

Abbreviations: ALL, acute lymphoblastic leukaemia; MA, marketing authorisation; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome

Decision problem

Link back to treatment pathway slide

	Final scope	Company and EAG comments
Comparators	Established clinical management without blinatumomab + chemotherapy, which may include: • chemotherapy (with or without corticosteroids) • allogenic stem cell transplant (alloSCT)	Company and EAG clinical experts considered alloSCT to not be a relevant comparator because: • alloSCT would be reserved for high-risk disease (e.g. with adverse cytogenetics) in population of relevance to this appraisal (subject to availability of a donor) • alloSCT would be received after induction/intensification therapy (prior to consolidation therapy), so blinatumomab would not displace alloSCT if recommended

Decision problem

	Final scope	Company	EAG comments
Outcomes	• **OS** • PFS (including **RFS** and EFS) • Treatment response rate • Rate of alloSCT • **AEs of treatment** • HRQoL (**Outcomes in bold** included in submission)	• Treatment response rate is not relevant because target population are already in complete remission and MRD-negative prior to consolidation therapy • Rate of alloSCT is not relevant in target population: ○ reserved for those with high-risk disease (subject to donor availability) and received prior to consolidation ○ intent to transplant was a stratification factor in E1910 → proportion who received alloSCT was low and balanced between arms, so treatment with blinatumomab did not influence having a transplant • HRQoL data was not collected in E1910	• OS, RFS and AEs are relevant endpoints • Treatment response is not relevant • Submission reports on the number of people who received alloSCT in each arm of E1910 ○ EAG's clinical experts → very few (if any) people with MRD-negative ALL would undergo alloSCT prior to relapse due to risk of treatment-related mortality

Abbreviations: AE, adverse event; ALL, acute lymphoblastic leukaemia; alloSCT, allogenic stem cell transplant; EFS, event-free survival; HRQoL, health-related quality of life; MRD, measurable/minimal residual disease; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival

E1910 results – OS and RFS censored at time of transplant

Results from full analysis set, MRD-negative population, primary analysis data cut-off June 2023

OS HR blinatumomab + chemotherapy vs chemotherapy

[redacted] (95% CI [redacted])
p-value = [redacted]

Median OS [redacted] in either arm

RFS HR blinatumomab + chemotherapy vs chemotherapy

[redacted] (95% CI [redacted])
p-value = [redacted]

Median RFS was [redacted] in chemotherapy arm and [redacted] in blinatumomab + chemotherapy arm

Abbreviations: CI, confidence interval; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival; RFS, relapse-free survival

Adverse events (AEs)

- Data based on safety analysis set which included all people who were randomised and received at least 1 dose of protocol-specific treatments (n=[redacted])
- Discontinuation due to AEs: n= [redacted] blinatumomab + chemotherapy arm, n= [redacted] chemotherapy alone
- No new safety signals were observed for blinatumomab + chemotherapy in E1910 trial

Grade ≥3 TEAEs (reported in ≥5% of participants)

- Overall frequency of grade ≥3 TEAEs were similar across both arms: ([redacted])

Most frequent grade ≥3 TEAEs	Blinatumomab + chemotherapy (n=[redacted])	Chemotherapy (n=[redacted])
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]

AEs of special interest

- Cytokine release syndrome: blinatumomab + chemotherapy ([redacted], grade ≥3: [redacted]) vs chemotherapy alone: ([redacted])
- Neurologic events: blinatumomab + chemotherapy ([redacted]) vs chemotherapy alone ([redacted])

Abbreviations: TEAE, treatment-emergent adverse event

Key Issue: Uncertainty around long-term OS and RFS (1)

Background – overall survival (1)

Link back to main slides on key issue

- For OS for both arms, company selected the Weibull MCM because it considered:
  - exponential, log-logistic and log-normal MCMs underestimated long-term survival compared to SMR-adjusted population mortality
  - Weibull MCM provided stable cure fractions when varied in the PSA, Gompertz MCM did not
  - generalised gamma MCM did not converge for OS, and so was excluded

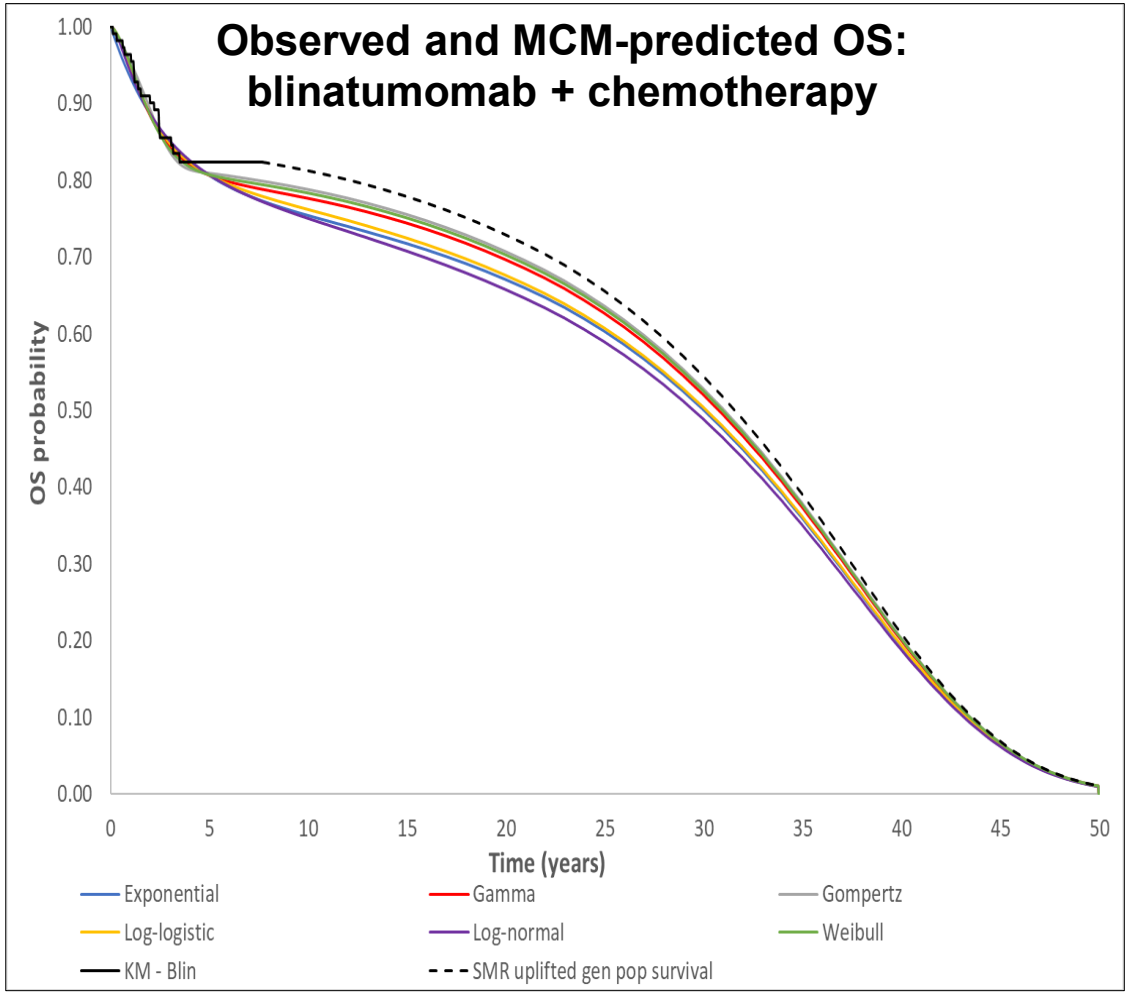
Mixture-cure model	Blinatumomab + chemotherapy			Chemotherapy		
	AIC (rank)	BIC (rank)	Estimated cure fraction	AIC (rank)	BIC (rank)	Estimated cure fraction
Exponential	253.67 (5)	259.11 (2)	0.781	464.91 (5)	470.35 (1)	0.278
Generalised gamma	250.42 (1)	261.29 (4)	-	465.23 (6)	476.10 (7)	-
Gompertz	250.62 (2)	258.77 (1)	0.823	465.54 (7)	473.69 (6)	0.540
Log-logistic	253.96 (6)	262.12 (6)	0.783	463.10 (1)	471.25 (2)	0.439
Log-normal	255.14 (7)	263.30 (7)	0.756	464.17 (4)	472.32 (5)	0.257
Weibull	**252.31 (3)**	**260.46 (3)**	**0.819**	**463.43 (3)**	**471.59 (4)**	**0.533**
Gamma	253.17 (4)	261.33 (5)	0.811	463.23 (2)	471.39 (3)	0.515

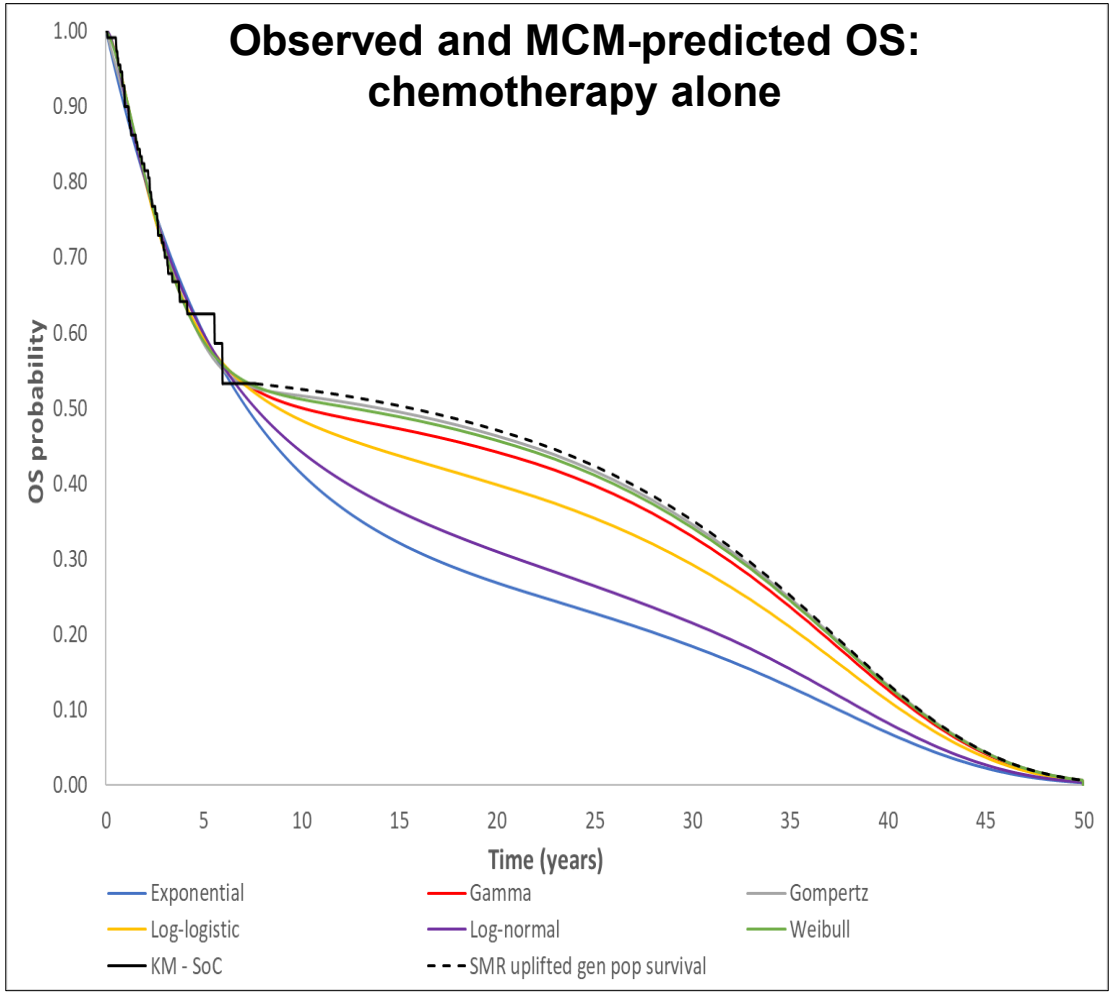
Abbreviations: AIC, Akaike Information Criterion; BIC; Bayesian Information Criterion; MCM, mixture-cure model; OS, overall survival; PSA, probabilistic sensitivity analysis; RFS; relapse-free survival; SMR, standardised mortality ratio

Key Issue: Uncertainty around long-term OS and RFS (2)

Background – overall survival (2)

Link back to main slides on key issue





Abbreviations: Blin, blinatumomab; KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; RFS, relapse-free survival; SoC, standard of care chemotherapy; SMR, standardised mortality ratio

Key Issue: Uncertainty around long-term OS and RFS (3)

Background – overall survival (3)

Link back to main slides on key issue

Landmark survival estimates for OS selected in base case and explored in company scenarios

Year	Blinatumomab + chemotherapy				Chemotherapy			
	KM	Weibull	Log-logistic	Gamma	KM	Weibull	Log-logistic	Gamma
1	96.4%	94.9%	94.7%	94.5%	90.0%	91.5%	91.5%	91.5%
2	90.1%	88.4%	88.6%	88.3%	81.5%	80.5%	79.9%	80.2%
3	85.5%	84.0%	84.7%	84.3%	70.0%	70.9%	70.7%	70.8%
4	82.4%	81.7%	82.3%	82.0%	64.1%	63.7%	64.0%	63.8%
5	82.4%	80.7%	80.7%	80.6%	62.5%	58.8%	59.3%	59.0%
10	-	78.3%	76.2%	77.6%	-	51.2%	48.4%	50.0%
20	-	70.2%	67.6%	69.6%	-	45.7%	39.8%	44.2%
30	-	52.4%	50.3%	51.9%	-	34.1%	29.2%	32.9%

- Company clinical expert supported the use of the Weibull MCM but considered long-term extrapolation in the chemotherapy group may be optimistic

EAG clinical expert comments

- Challenging to select a preferred model for OS → model predictions using Weibull MCM are reasonable
- Log-normal and exponential MCMs for OS in the chemotherapy group appear to be overly pessimistic

Abbreviations: KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; RFS, relapse-free survival

Key Issue: Uncertainty around long-term OS and RFS (4)

Background – relapse-free survival (1)

Link back to main slides on key issue

- For RFS for both arms, company selected the log-normal MCM because it considered:
  - Gompertz MCM resulted in unstable cure fractions during PSA, and so was excluded
  - generalised gamma MCM appeared to over-fit RFS data, provided low cure fractions and did not converge for OS, and so was excluded
  - all remaining MCMs resulted in similar statistical and visual fit to trial data for both arms, but 1) underestimated RFS towards the tail of the KM curve for blinatumomab + chemotherapy arm and 2) overestimated RFS towards the tail of the KM curve for chemotherapy arm
    - ➢ log-normal MCM overestimates 2) to a lesser degree than other models

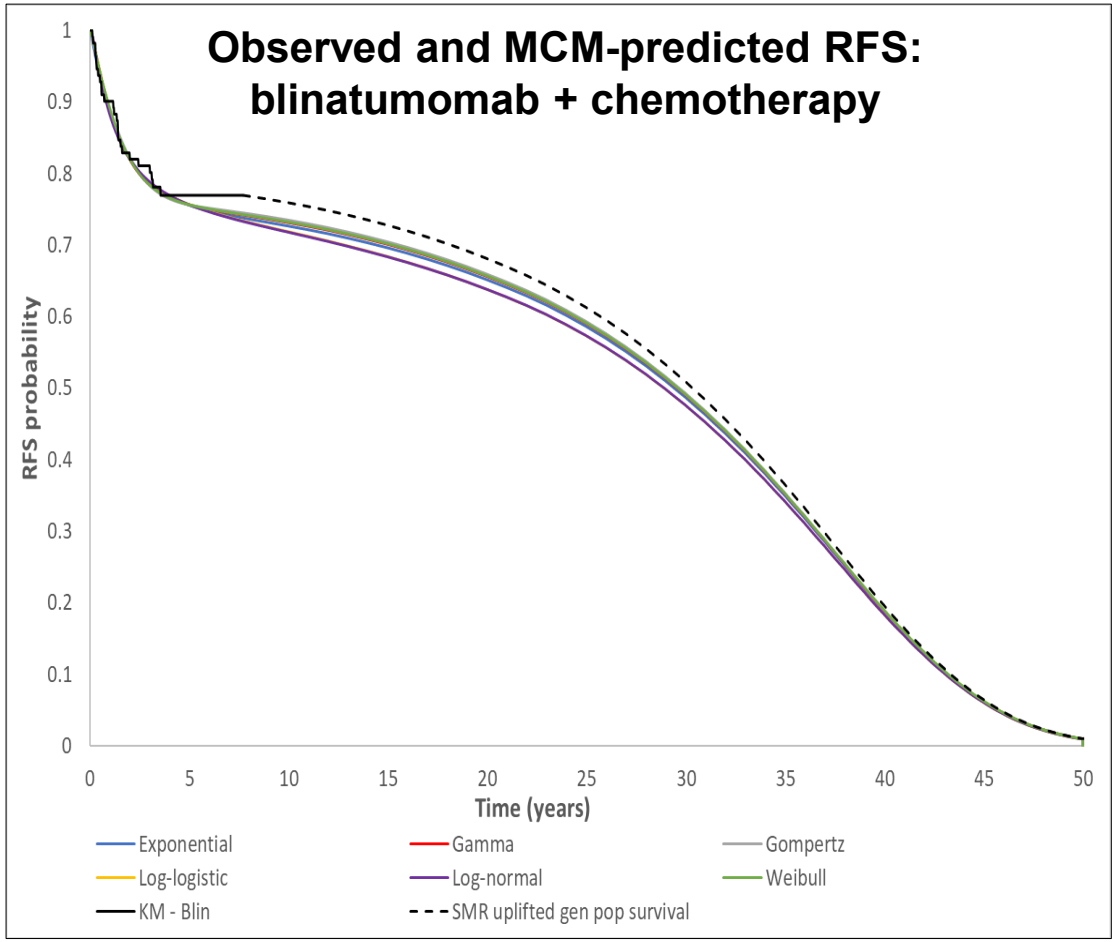
Mixture-cure model	Blinatumomab + chemotherapy			Chemotherapy		
	AIC (rank)	BIC (rank)	Estimated cure fraction	AIC (rank)	BIC (rank)	Estimated cure fraction
Exponential	306.9 (1)	312.3 (1)	0.759	478.0 (2)	483.4 (1)	0.528
Generalised gamma	309.5 (7)	320.4 (7)	-	478.3 (4)	489.2 (7)	-
Gompertz	308.4 (5)	316.6 (5)	0.768	479.7 (6)	487.9 (5)	0.425
Log-logistic	308.5 (6)	316.7 (6)	0.737	478.1 (3)	486.2 (3)	0.486
Log-normal	**307.6 (2)**	**315.8 (2)**	**0.740**	**476.8 (1)**	**485.0 (2)**	**0.465**
Weibull	308.4 (4)	316.5 (4)	0.765	479.8 (7)	488.0 (6)	0.540
Gamma	308.2 (3)	316.4 (3)	0.764	479.6 (5)	487.7 (4)	0.544

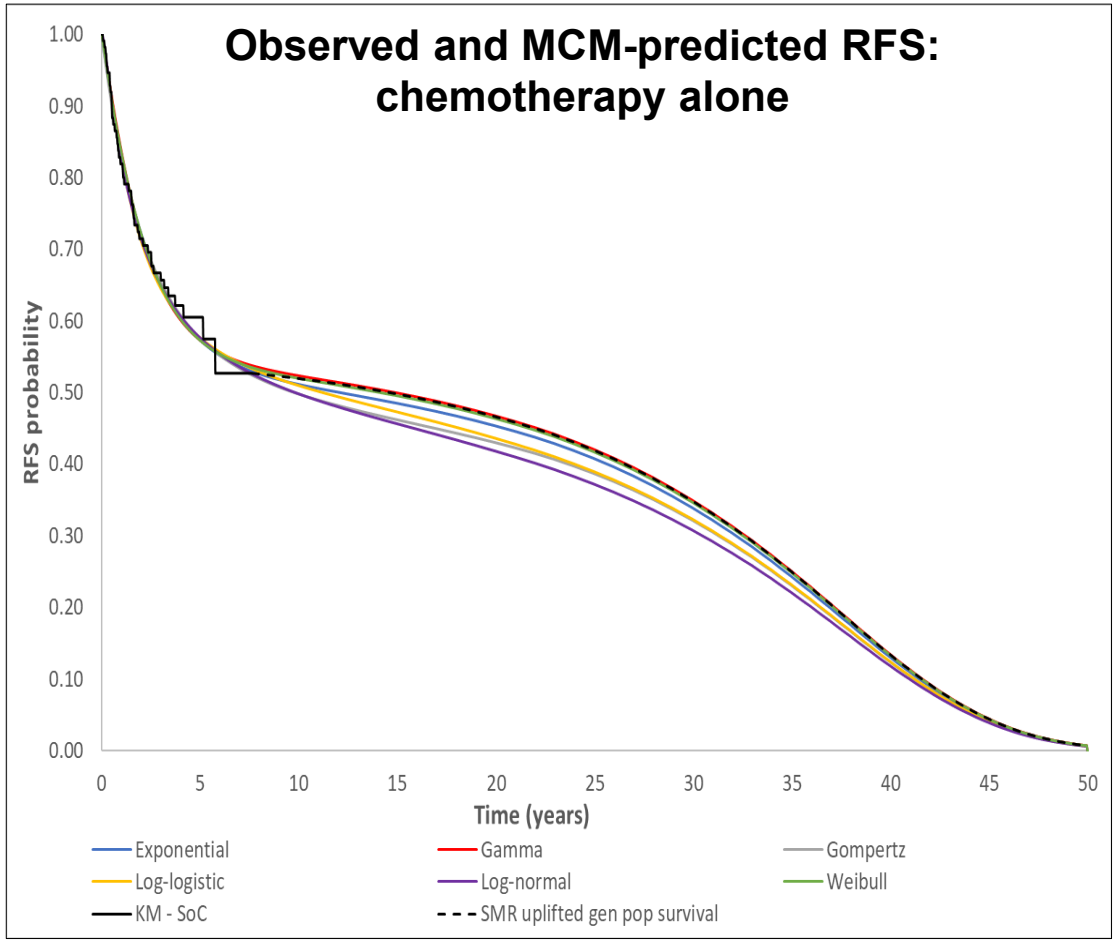
Abbreviations: AIC, Akaike Information Criterion; BIC; Bayesian Information Criterion; KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; PSA, probabilistic sensitivity analysis; RFS, relapse-free survival

Key Issue: Uncertainty around long-term OS and RFS (5)

Background – relapse-free survival (2)

Link back to main slides on key issue





Abbreviations: Blin, blinatumomab; KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; RFS, relapse-free survival; SoC, standard of care chemotherapy; SMR, standardised mortality ratio

Key Issue: Uncertainty around long-term OS and RFS (6)

Background – relapse-free survival (3)

Link back to main slides on key issue

Landmark survival estimates for RFS selected in base case and explored in company scenarios

Year	Blinatumomab + chemotherapy				Chemotherapy			
	KM	Log-normal	Exponential	Log-logistic	KM	Log-normal	Exponential	Log-logistic
1	90.1%	87.9%	88.3%	88.1%	81.9%	82.2%	83.0%	82.4%
2	82.0%	81.9%	82.1%	81.9%	71.5%	71.4%	72.2%	71.0%
3	81.1%	78.8%	78.7%	78.8%	65.7%	64.9%	65.1%	64.5%
4	77.0%	76.9%	76.7%	76.9%	62.1%	60.6%	60.4%	60.4%
5	77.0%	75.6%	75.5%	75.6%	60.5%	57.6%	57.3%	57.6%
10	-	71.8%	72.6%	71.8%	-	49.8%	51.1%	51.0%
20	-	63.8%	65.1%	63.8%	-	41.8%	45.3%	43.6%
30	-	47.5%	48.6%	47.5%	-	30.7%	33.8%	32.2%

- Company clinical expert supported the use of the log-normal MCM but considered long-term extrapolation in the chemotherapy group may be optimistic

EAG clinical expert comments

- Challenging to select a preferred model for RFS → model predictions using log-normal MCM are reasonable

Abbreviations: KM, Kaplan-Meier; MCM, mixture-cure model; OS, overall survival; RFS, relapse-free survival