Lead team presentation
Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982] – STA

1st Appraisal Committee meeting

Committee C

Lead team: Derek Ward and David Chandler

ERG: CRD and CHE Technology Assessment Group, University of York,

Technical team: Julia Sus, Nicola Hay and Alex Filby

26 April 2018

Key Issues - clinical (1)

Decision problem

- Is it appropriate for the company to focus its submission to patients not known to have unfavourable cytogenetics?
- Would the requirement for cytogenetic test results before the start of treatment with GO potentially delay the start of treatment?

Clinical Pathway

- Is it routine practice in the NHS in England to undertake cytogenetic testing before the start of treatment?
- How long does it take routinely for cytogenetic results to be reported?
- Is molecular testing undertaken routinely? If so in what circumstances?
- Which group of patients would GO be used in?

Key Issues – clinical (2)

ALFA-0701 trial:

- Dose used in the trial is different to that being used in clinical practice through the AML18 and AML19 trials. What implications does this have for dosing in clinical practice?
- Is it appropriate to assume patients are functionally cured if there are no events in 3 years of treatment response?
- How robust are the data for patients with an unfavourable cytogenetic profile?
- How important is this heterogeneity in the broader 'intermediate' cytogenetic subgroup?

IPD meta-analysis

- How generalisable are the results from the IPD meta-analysis to patients eligible for GO + DA in clinical practice in England?

Disease Background

- Acute myeloid leukaemia has one of the lowest survival rates among leukaemias
- The incidence of acute myeloid leukaemia in England is about 3,000 people per year
- Around 55% of all cases occur in people over 70 years
- There were 2471 new diagnoses of AML in England.
- AML is primarily a disease in older people, with incidence rising gradually from 40–44 years of age and then more steeply from 55–69 years of age.
- In 2014, there were around 2,516 deaths from AML in the UK

Source: company submission pages 18-25

Gemtuzumab Ozogamicin (Pfizer)

Marketing authorisation	Committee for Medicinal Products for Human Use (CHMP) opinion received February 2018 Indicated in combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).
Final scope issued by NICE*	People aged 15 years and older with untreated, de novo CD33-positive acute myeloid leukaemia (AML) (excluding acute promyelocytic leukaemia)
Company's decision problem	Adult patients not known to have unfavourable cytogenetics, with previously untreated, de novo AML

* Revised final scope issued following up-date from company regarding the expected wording of the marketing authorisation and following CHMP positive opinion. Population extended to include people aged 15-17 years and restricted to de novo CD33-positive AML. Revised final scope issued after the company had provided its submission to NICE and during the completion of the ERG report.

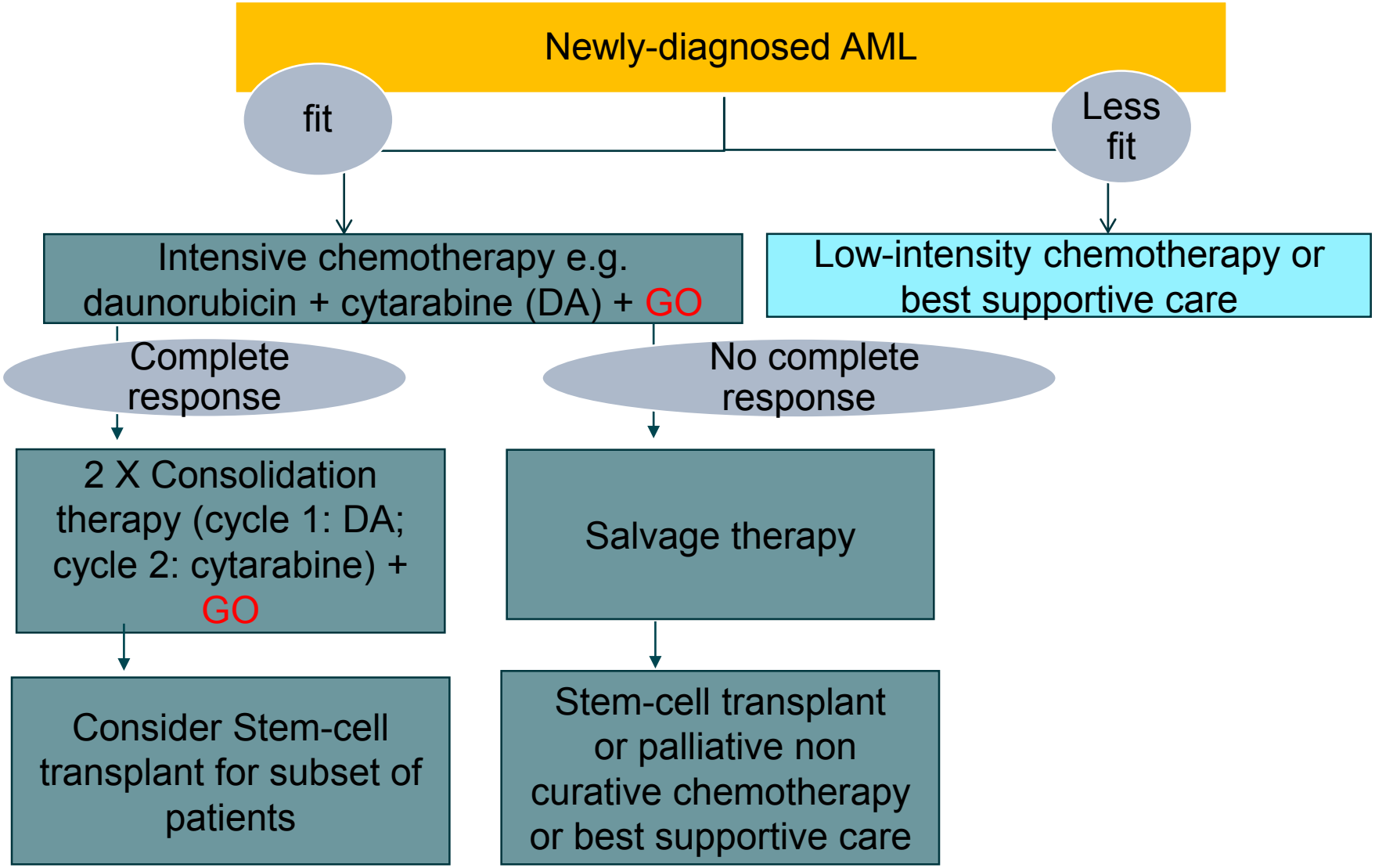
ERG's comments: Population in company's decision problem

- Population addressed in the company's decision problem is a subpopulation of the anticipated marketing authorisation for gemtuzumab ozogamicin and the final scope issued by NICE
- Company's decision problem excludes patients known to have unfavourable cytogenetics as they would not receive treatment with gemtuzumab ozogamacin plus intensive chemotherapy in NHS clinical practice.
    - The clinical advisor to the ERG supported the company's rationale for excluding patients with unfavourable cytogenetics.
    - In view of the very short timeframe between diagnosis and treatment in patients with AML, the requirement for cytogenetic test results before treatment could potentially delay the start of treatment with gemtuzumab ozogamicin
- The restriction to CD33-positive AML in the CHMP positive opinion is a narrower population than that addressed in the company's decision problem

Source: ERG report, page 25

Clinical pathway of care

BCSH guidelines recommend that patients are enrolled in a clinical trial, those who are unable to participate in trial, should be offered intensive therapy with DA.



Related NICE Guidance

Published

TA399	Azacitidine not recommended, within its marketing authorisation, for treating AML with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant
TA218	Azacitidine recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have AML with 20–30% blasts and multilineage dysplasia

In development

ID894	Midostaurin for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive

Patient perspective (1)

Living with untreated acute myeloid leukaemia (AML)

(Leukaemia Care submission)

- Rapidly progressing condition
- 54% experience symptoms for less than a month before visiting GP
- Symptoms following diagnosis include:
  - *Fatigue (73%),*
  - *Weakness/breathlessness (51%),*
  - *Bruising or bleeding easily (37%)*
- Daily routines also affected including:
  - *Difficulty moving around and performing everyday tasks, such as, cooking and cleaning*
  - *Difficult to continue to work or stay in education*
- Following diagnosis patients report:
  - *A huge emotional impact,*
    - with feelings of disbelief, denial, anger and depression.
  - *Huge emotional strain on families*

Patient perspective (2)
View of current treatments

- There has been limited progress in AML
- Urgent improvement needed
- High unmet need
- Gemtuzumab ozogamicin has a series of side effects
- 80% of AML patients reported they are willing to experience additional side effects for a more effective treatment

Comments from professional groups

- Gemtuzumab ozogamicin appears to improve overall survival when added to induction chemotherapy for patients with favourable and intermediate risk disease karyotype
- There is need to access cytogenetic results very promptly at diagnosis before starting treatment, which is not a standard practice
- Gemtuzumab ozogamicin would be added to standard induction chemotherapy in newly-diagnosed AML
- Highly innovative, it will be the first routine application of antibody-directed chemotherapy in the treatment of AML

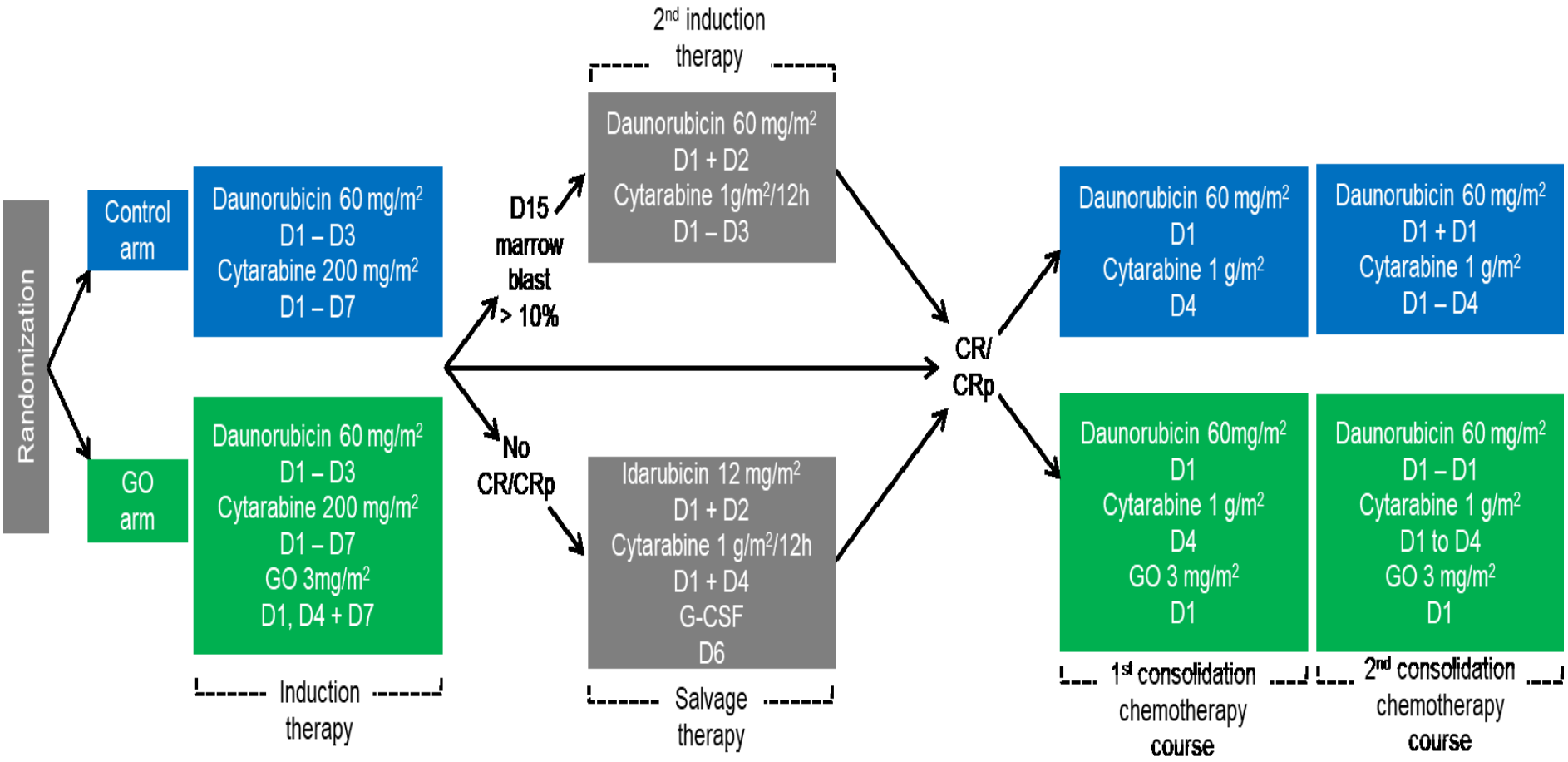
NHS England's Comments

- NHS England notes that the company submission restricts the population of patients from that included in the marketing authorisation.
- CD33 testing for acute leukaemia is part of the diagnostic portfolio of routine testing and is known prior to any AML chemotherapy being started.
- Cytogenetics is done on all AML cases. It provides important prognostic information and informs treatment options. There is great emphasis placed in obtaining cytogenetic results as quickly as possible, it can take between a few days (larger centres) and 3 weeks (smaller centres).
- NHS England accepts that patients requiring urgent therapy would be started on GO upfront. In those who have poor risk disease, NHS England sees no reason for GO to be continued beyond the 1st cycle of induction chemotherapy, if such decision is made by NICE TA committee. Any costs GO incurred in this situation must be included in the health economic analysis.
- NHS England would wish the costs of veno-occlusive disease treatment to be included in the technology appraisal, together with defibrotide.
- If NICE recommends GO in the treatment of previously untreated AML, NHS England will extend its commissioning to patients under the age of 15 years, in line with marketing authorisation.

Company's evidence of clinical effectiveness

Evidence	Source	Used in clinical effectiveness	Used in cost effectiveness
ALFA-0701 trial	CS pages 38-79; ERG report pages 30-45	main evidence	Yes
Additional analysis by IRC assessment for EFS, RFS, OS and molecular status	Company's response to clarification; ERG report pages 44-47	Yes	Yes
Individual patient data (IPD) meta-analysis (uses evidence from ALFA-0701 and 4 other trials)	CS page 74 and, also Appendix D.3.1; ERG report pages54-60	supportive evidence	No (different and unlicensed dosing regimens in the other trials)
Published meta-analysis	CS (Appendix D.3.2); ERG report pages 60-61	supportive evidence	No
Abbreviations: CS, Company submission			

Company's clinical evidence:
ALFA-0701 trail



- Multi-centre, phase 3, randomised 1:1, open-label, comparing GO + DA versus DA alone in patients aged 50–70 years of age with de novo, untreated AML

Baseline characteristics in ALFA-0701(1)

modified intention to treat (mITT) population

Characteristic	GO+DA (n=135)	DA (n=136)
Age, years, median (range)	62.0 (50–70)	61.0 (50–70)
< 60, n (%)	38 (28.1)	52 (38.2)
≥ 60, n (%)	97 (71.9)	84 (61.8)
Male, n (%)	74 (54.8)	60 (44.1)
ECOG PS, n (%)		
0–1	121 (89.6)	117 (86.0)
≥ 2	14 (10.4)	18 (13.2)
Missing	0 (0.0)	1 (0.7)
WBC count,×109/L, median (IQR)	5.8 (0.5–151.0)	4.1 (0.1-180.5)
Cytogenetics, n (%)		
Favourable	3 (2.2)	6 (4.4)
Intermediate	91 (67.4)	89 (65.4)
Unfavourable	27 (20.0)	30 (22.1)
Not available	14 (10.4)	11 (8.1)
CD33 expression, positivity		
< 30%	17 (12.6)	20 (14.7)
≥ 30%	83 (61.5)	74 (54.4)
< 70%	37 (27.4)	31 (22.8)
≥ 70%	63 (46.7)	63 (46.3)

Baseline characteristics in ALFA-0701(2)

modified intention to treat (mITT) population

Characteristic	GO+DA arm (n=135)	DA arm (n=136)
***NPM1* status, n (%)**		
Mutated	35 (25.9)	33 (24.3)
Wild type	37 (27.4)	33 (24.3)
Unknown	1 (0.7)	9 (6.6)
Not available	62 (45.9)	61 (44.9)
FLT3-ITD status, n (%)		
Mutated	16 (11.9)	16 (11.8)
Wild type	56 (41.5)	51 (37.5)
Unknown	1 (0.7)	8 (5.9)
Not available	62 (45.9)	61 (44.9)
CEBPA status, n (%)		
Mutated	5 (3.7)	6 (4.4)
Wild type	65 (48.1)	55 (40.4)
Unknown	3 (2.2)	14 (10.3)
Not available	62 (45.9)	61 (44.9)

ERG's comments: ALFA-0701 trial

Area	ERG's comments
Study population	The anticipated marketing authorisation for GO specifies patients with CD33-positive AML, whilst the trial also included AML patients who were not CD33-positive, therefore, a small proportion of patients in the trial would not be eligible for GO + DA in clinical practice.
	The trial included only patients aged 50-70 years, whilst the anticipated marketing authorisation includes patients age 15 years and above; however, the majority of patients diagnosed with AML are over 50 years of age, therefore the population included in the trial is likely to be reflective of the majority of patients eligible for GO in clinical practice
Outcome	• HRQoL was not assessed in the ALFA-0701 trial. • Patients may relapse later than 5 years, longer term events may not have been captured in the ALFA-0701 trial data. • Cytogenetic test results could potentially delay start of the treatment
Dosing schedule	Dosing schedule in the ALFA-0701 trial is in line with the anticipated marketing authorisation, however two ongoing trials which include UK treatment centres use different dosing regime.

Overall the trial was well conducted and has a low risk of bias, up to the limits of its open-label design.

Overall survival-April 2013 data cut-off

modified intention to treat (mITT) population

Event-Free survival-April 2013 data cut-off

modified intention to treat (mITT) population

Relapse-Free survival-April 2013 data cut-off

modified intention to treat (mITT) population

Summary of efficacy endpoints in ALFA-0701(1)

mITT population; 30 April 2013 data cut-offs; IRC assessment

	GO + DA arm	DA arm	HR (95% CI) P-value
EFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
RFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
OS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
Overall response rate (CR/CRp), n (%)	[redacted]	[redacted]	

Abbreviation: IRC assessment, independent review committee; CR/CRp, complete remission/CR with incomplete platelet recovery; EFS, event-free survival; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; OR, odds ratio; mITT, modified intention to treat

To properly understand the efficacy of GO some further breakdown by cytogenetic status is required

Summary of efficacy endpoints in ALFA-0701 (2)

by cytogenetics profile (mITT population) using the 30th April 2013 data cut-off

1. Patients with favourable/intermediate cytogenetic profile

	GO+DA arm (n=94)	DA arm (n=95)	HR (95% CI)
EFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
RFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
OS months, median (95% CI)	[redacted]	[redacted]	[redacted]
Overall response rate (CR/CRp), n (%) [IRC analysis data]	[redacted]	[redacted]	[redacted]

Abbreviation: IRC assessment, independent review committee ;CR/CRp, complete remission/CR with incomplete platelet recovery; EFS, event-free survival; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; OR, odds ratio

Summary of efficacy endpoints in ALFA-0701 (3)

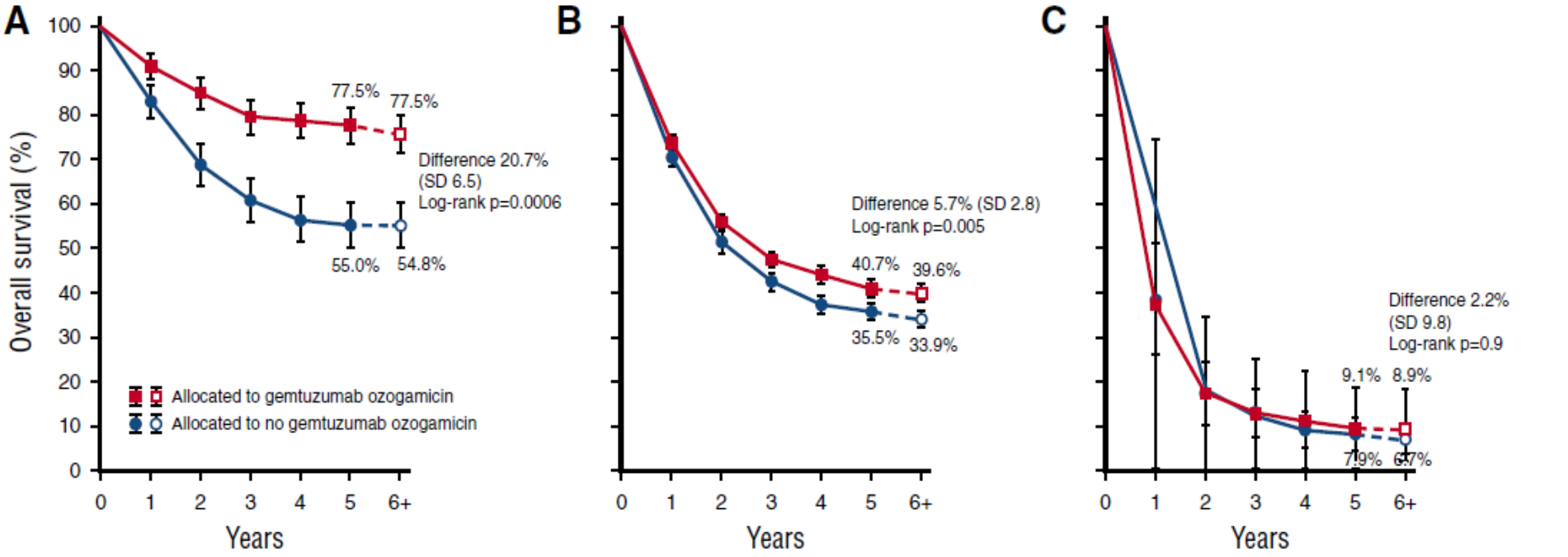
by cytogenetics profile (mITT population) using the 30th April 2013 data cut-off

2. Patient with unfavourable cytogenetic profile (IRC analysis data)

	GO+DA arm (n=27)	DA arm (n=30)	HR (95% CI)
EFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
RFS, months, median (95% CI)	[redacted]	[redacted]	[redacted]
OS, months, median (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviation: IRC assessment, independent review committee EFS, event-free survival; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio;

Overall survival stratified by cytogenetic risk category



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No Gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No Gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No Gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

(A) OS of 246 patients with favourable-risk AML. (B) OS of 1827 patients with intermediate-risk AML. (C) OS of 583 with adverse-risk disease.

Source: Frederick R. Appelbaum and Irwin D. Bernstein et al, Gemtuzumab ozogamicin for acute myeloid leukemia Blood 2017 :blood-2017-09-797712

Analysis by cytogenetic and molecular status (1)

Summary of EFS, months, median (95% CI) by cytogenetic/molecular subgroup (IRC analysis)

Cytogenetic/molecular profile	GO + DA arm	DA arm	Point estimate (95% CI)
Intermediate-1 [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2 [redacted]	[redacted]	[redacted]	[redacted]
Favourable/intermediate-1 [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2/unfavourable [redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: EFS, event-free survival; IRC, independent review committee

Analysis by cytogenetic and molecular status (2)

Summary of RFS (IRC analysis), months, median (95% CI) by cytogenetic/molecular subgroup

Cytogenetic/molecular profile	GO + DA arm	DA arm	Point estimate (95% CI)
Intermediate-1 [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2 [redacted]	[redacted]	[redacted]	[redacted]
Favourable/intermediate-1 [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2/unfavourable [redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: RFS, relapse-free survival; IRC, independent review committee

*[redacted]

OS analysis by cytogenetic and molecular subgroup

Summary of OS (IRC analysis): months, median (95% CI)

Cytogenetic/molecular profile	GO + DA	DA	Point estimate (95% CI)
Intermediate-1 (months [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2 [redacted]	[redacted]	[redacted]	[redacted]
Favourable/intermediate-1 [redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2/unfavourable [redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: OS, overall survival; IRC, independent review committee

Summary of AEs and SAEs

	GO + DA, (N = 131) n (%)		DA, (N = 137) n (%)	
	All-causality AEs	Related AEs	All-causality AEs	Related AEs
Patients with Aes	[redacted]	[redacted]	[redacted]	[redacted]
Patients with SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with grade 3 or 4 or severe infection AEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with fatal events	[redacted]	[redacted]	[redacted]	[redacted]
Patients who permanently discontinued study	[redacted]	[redacted]	[redacted]	[redacted]

Veno-occlusive disease (VOD)	**GO+DA, (N=131), n (%)**	**DA, (N=137), n (%)**
Proportion of patients with VOD	[redacted]	[redacted]

ERG's additional comments on company's clinical evidence

Company subgroup analysis by cytogenetic status

- Results better for the subgroup with favourable/intermediate cytogenetic risk, than the overall population
- Population with unfavourable cytogenetics, appeared to have worse outcomes in the GO + DA treatment arm, compared with the DA treatment arm.

Additional subgroup analysis by cytogenetic and molecular status requested at clarification

- [redacted]
- [redacted]

The individual patient data (IPD) meta-analysis

- Included patients aged 15 years or older with newly diagnosed AML (either de novo or secondary), or high-risk myelodysplastic syndrome (MDS)
- Broader population than that defined in the decision problem or the anticipated marketing authorisation. Results may not be entirely generalisable to people eligible to receive GO in clinical practice

Key Issues - clinical (1)

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- Would the requirement for cytogenetic test results before the start of treatment with GO potentially delay the start of treatment?

Clinical Pathway

- Is it routine practice in the NHS in England to undertake cytogenetic testing before the start of treatment?
- How long does it take routinely for cytogenetic results to be reported?
- Is molecular testing undertaken routinely? If so in what circumstances?
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Key Issues – clinical (2)

ALFA-0701 trial:

- Dose used in the trial is different to that being used in clinical practice through the AML18 and AML19 trials. What implications does this have for dosing in clinical practice?
- Is it appropriate to assume patients are functionally cured if there are no events in 3 years of treatment response??
- How robust are the data for patients with an unfavourable cytogenetic profile?
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Lead team: Nigel Langford

ERG: CRD and CHE Technology Assessment Group, University of York,

Technical team: Julia Sus, Nicola Hay and Alex Filby

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Key issues – cost effectiveness (1)

- Is the company's model appropriate for decision making given its complexity?
- Is the absence of an explicit structural link between relapse and HSCT appropriate?
- Should the initial treatment costs of the induction and consolidation therapies be based on the IA response outcomes or on an adjustment of the IRC response outcomes as proposed by the company?
- Is it appropriate to pool response data?
- What is the most appropriate HR for long-term morbidity and survival for functionally cured patients?
- Is it appropriate to assume that functionally cured patients experience the same HRQoL as the general population?
- Are the costs for HSCT included in the company's model appropriate?
- Is it appropriate to include patients with VOD in the DA treatment arm in the model?
- Has the additional inpatient treatment costs associated with VOD been adequately captured in the company's model?

Key issues - cost effectiveness and other (2)

Cost effectiveness

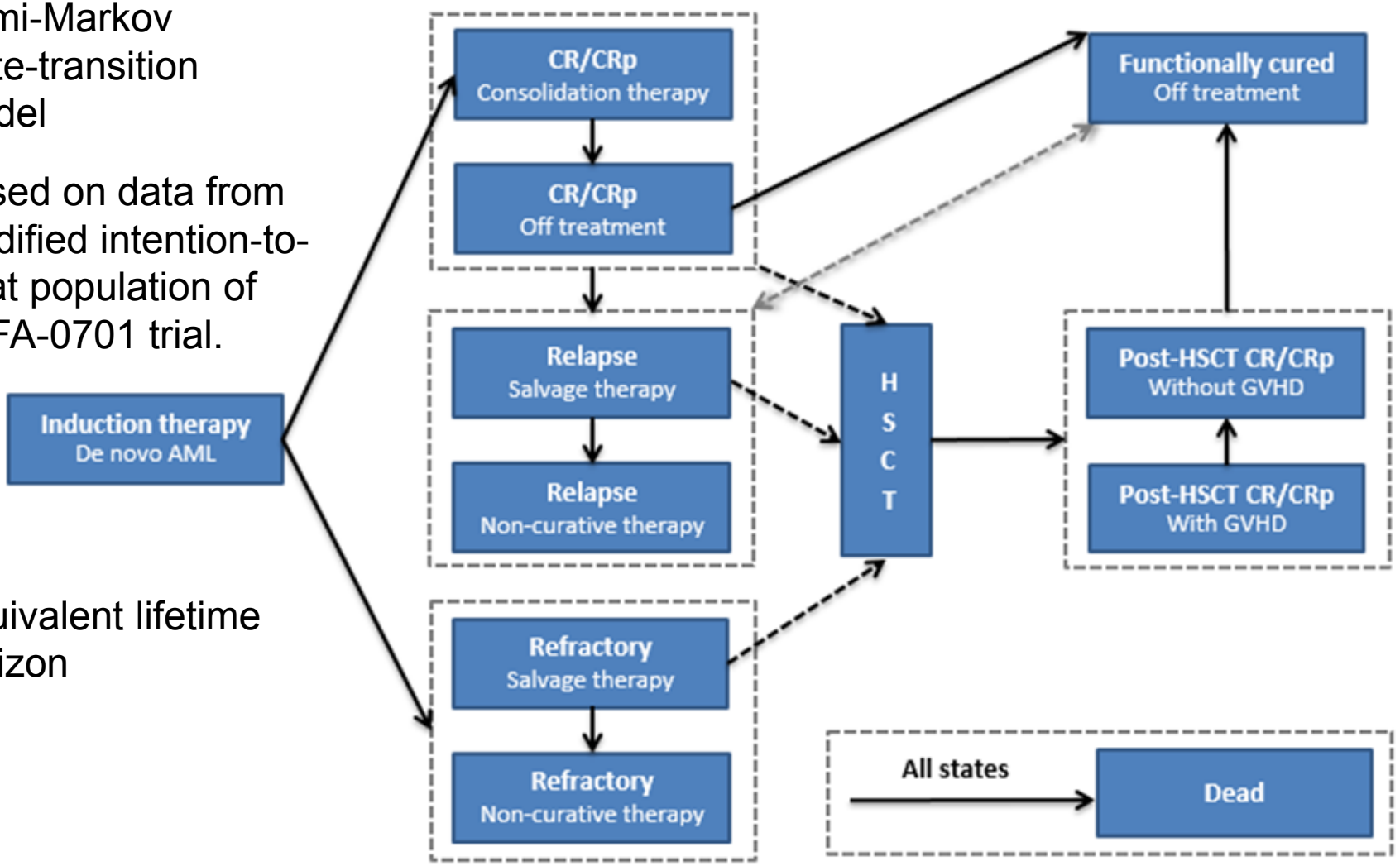
- What are the implications of the heterogeneity in the subgroup of patients with unknown cytogenetics and within the intermediate population on the most plausible ICER?
- What is the most plausible ICER?

Other

- Is gentuzumab ozogamicin an innovative treatment?
- Are there any equality issues?

Company's economic model

- Semi-Markov state-transition model
- Based on data from modified intention-to-treat population of ALFA-0701 trial.
- Equivalent lifetime horizon



Company's model: Summary (1)

Input	Source/assumption
Population	Base-case: based on a subgroup of population in the CHMP positive opinion - patients not known to have unfavourable cytogenetics. Results also presented separately for the entire licensed population
Intervention/ comparator	Gentuzumab ozogamicin in combination with standard intensive chemotherapy, consisting of daunorubicin and cytarabine (DA) compared with DA alone
Treatment effectiveness	Clinical outcomes included: response (CR/CRp), RFS and OS, cure fraction, probability of HSCT, HSCT cure fraction Patients alive or relapse-free at 60 months post induction therapy or HSCT assumed to be cured and experienced general population mortality adjusted to reflect excess mortality in AML survivors
	Data taken from ALFA-0701. OS stratified by response status and parametric models fitted to extrapolate beyond the end of the trial follow-up. Parametric models fitted to RFS (CR/CRp only)
	Response and RFS endpoints based on the blinded IRC assessment, RFS and OS based on reference data 30 April 2013

Abbreviation: HSCT, haematopoietic stem cell transplantation; RFS, relapse-free survival; IRC, independent review committee; CR/CRp, complete remission/CR with incomplete platelet recovery; OS, overall survival

Company's model: Summary (2)

Input	Source/assumption
Adverse Events	taken from ALFA-0701, Grade 3 and 4 treatment related events that occurred in at least 1% of patients GVHD as a consequence of HSCT also included. Incidence of GVHD sourced from external literature.
HRQoL	No HRQoL data collected in ALFA-0701. Health state utility values sourced from a systematic literature review: • Functionally cured patients assumed to have QoL equal to that of the aged-matched general population • Remaining utilities sourced from NICE TA399, except for post-HSCT CR/CRp with GVHD sourced from Kurosawa (2016) • Adverse event disutilities sourced from NICE TA399, except for VOD (appraisal of exdefibrotide by the SMC) A vignette study undertaken by the company provided 2 alternate sets of utility values that were used in scenarios

Abbreviation: GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; HRQoL, health-related quality of life; CR/CRp, complete remission/CR with incomplete platelet recovery; VOD, veno-occlusive disease

ERG's comments: Company's model

Model structure

- There is a lack of an explicit structural link between a number of key model parameters, most importantly between relapse and HSCT
- The absence of a structural link restricts the ability of the model to explore alternative scenarios in an appropriate manner, and, therefore, to fully capture the uncertainty in the modelled results
- The model structure is complex and challenging to critique given the difficulties in determining the actual flow of patients through the model

Population modelled

- Company did not adequately explore any remaining heterogeneity within the intermediate population and the possible implications for clinical and cost-effectiveness
- Company did not sufficiently justify the inclusion of the subgroup with unknown cytogenetics. Additional analysis provided in response to clarification showed that excluding this population from cost-effectiveness resulted increased the ICER

Company’s model: Predicted OS (CR)

Company's model: OS in refractory patients

Company’s model: Relapse-free survival

Summary of survival functions in company's base-case analysis

End point	GO+DA	DA	Pooled
RFS (CR or CRp)	MCM log-normal Cure rate: [redacted]	MCM log-normal Cure rate: [redacted]	
OS (CR or CRp)	MCM log-normal Cure rate: [redacted]	MCM log-normal Cure rate: [redacted]	
OS (refractory)	-	-	Gompertz Cure rate: n/a

CR, complete remission; CRp: complete remission with incomplete platelet recovery; GO, gemtuzumab ozogamicin; OS, overall survival; RFS, relapse-free survival; MCM, mixed cure model

ERG's comments: Company's survival functions

- Overall, the ERG considered the approach to curve fitting and the rationale for selecting distributions to be appropriately justified

- Although the alternative MCM distributions reported different estimates of the absolute cure fraction for each group, difference in the cure fraction between the groups was broadly similar for both the MCM lognormal and Weibull functions for both EFS and OS. This is important because it is the difference between the groups in the probability of long-term survival which is the main driver of QALY differences and the ICER estimates

- The choice of survival function for the base-case population, is less critical than the assumptions which are subsequently applied to long-term survivors regarding potential excess morbidity (HRQoL assumptions) and mortality

Company's model: Mortality in the cured population

- Company used a HR of [redacted] to capture the excess mortality (relative to the general population) for functionally cured patients at 5 years
- HR based on the company's analysis of pooled survival data from UK AML trials 10 to 16, restricted to patients with de novo AML with intermediate and favourable cytogenetics aged 50 to 70, using survival curves conditional on surviving the first 5 years
- HR estimated by calculating the ratio of the means of annual mortality rates, from 5 years after AML diagnosis and of those matched to the mean age of the analysis from the general population
- Excess mortality HR applied after the cure point at 5 years, and was applied to patients considered to be cured after consolidation therapy as well as HSCT

ERG's comments: Mortality in the cured population

- ERG was generally satisfied with the manner in which it was implemented
- However uncertainties remain regarding the estimation of the adjustment factor (HR):
  - Number of patients at risk in the analysis of AML10-16 trial data not reported and therefore difficult to determine how robust the estimates of mortality are in later years. Values may be based on small patient numbers.
  - The HR per cycle higher in the years immediately following year-5 before settling into a more consistent pattern.
  - In some years, the probability of death was higher in the general population than in survivors with AML, which does not seem plausible

Company's model and ERG critique: HSCT

Company's model

- Patients able to receive HSCT from 3 health states: CR/CRp, refractory, and relapsed
- Probabilities of receiving HSCT estimated from data of patients receiving HSCT in ALFA-0701, excluding those with unfavourable cytogenetics

ERG's comments

- Company limited complexity of model by including additional structural assumptions for the HSCT state and using calendar time rather than time in state as well as absolute probabilities at fixed times. These assumptions ensured that the model predicted identical HSCT rates as observed in the trial
- Main uncertainty was whether the data from the trial was sufficiently mature to provide an accurate estimate of the long-term difference in HSCT rates between the 2 treatment arms. Additional data and Kaplan-Meier curves provided in response to clarification suggested no obvious bias or differences in the time at risk
- However, the ERG noted that some of the cost-off sets for HSCT are predicted on the functional assumption. The absence of any structural link to HSCT rates limited the ERG's ability to further assess the potential impact of this source of uncertainty

Company's model: Health-related quality of life

Utility state	Values used in base–case analysis	Values used in scenario analysis		
Source	TA399	TA399	Pfizer TTO	Pfizer VAS
Chemotherapy treatment[1]	0.66	0.72	[redacted]	[redacted]
Consolidation treatment	0.66	0.72	[redacted]	[redacted]
HSCT	0.66	0.72	[redacted]	[redacted]
GVHD (post-HSCT)	0.67[3]	0.67[3]	[redacted]	[redacted]
CR/CRp off-treatment	0.74	0.77	[redacted]	[redacted]
Relapse	0.57	0.62	[redacted]	[redacted]
Refractory	0.57	0.62	[redacted]	[redacted]
Functionally cured	0.82[2]	0.82[2]	[redacted]	[redacted]

1.Applied to patients in induction, salvage and non-curative
2.Varied per cycle, based on mean patient age at each time point, from Ara & Brazier
3.Source Kurosawa 2016

ERG's comments: Health-related quality of life

- ERG considered the approach used by the company to be reasonable and appropriately justified.

- Company's assumption that functionally cured patients experience the same HRQoL as the general population results in a marked jump in the HRQoL estimates at 5-years for functionally cured patients

- Use of general population quality of life was not internally consistent with the excess mortality applied for functionally cured patients to OS. Given functionally cured patients are assumed to be at higher mortality risk than the general population, it would be reasonable to assume that functionally cured patients would also have lower quality of life than that of the general population

Company's costs and resource use untreated disease

- Treatment costs (company base case assumption: similar proportion receiving induction and consolidation therapy across treatment groups and no drug wastage in line with clinical expert input)
- Subsequent lines of therapy (salvage and non-curative)
- HSCT costs (one-off cost and monthly costs up to 2 years and transplant-related acute and chronic GVHD complications)
- Health state costs in line with clinical expert input (including inpatient and outpatient attendances, consultant haematologist; specialist nurse; disease monitoring tests, supportive therapies and blood products)
- Grade 3 and 4 adverse events (including skin toxicity, venous occlusive disease, mucosal toxicity
- End of life costs for patients receiving non-curative therapy (including best supportive care).

Company's base-case results: excluding unfavourable cytogenetics

- Company included people with unknown cytogenetics in the base-case population

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
Deterministic results					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£12,251
DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,600
DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's sensitivity analyses showed that HSCT probabilities from relapse in years 1 and 2 for the DA group, and the RMST for relapsed patients had the greatest impact on the ICER

Company's cost effectiveness analysis: All patients

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	20,457
DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: Inc., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; GO, gemtuzumab ozogamicin; DA, daunorubicin + cytarabine

ERG's amendments to company's base-case

- Inconsistencies in the data source for mortality: ERG incorporated the more recently published mortality data for England & Wales for the survival analysis, and the mortality data for the UK for the mortality HR calculations.
- Discrepancy for HSCT probabilities after relapse: ERG amendment involved changing the calculations to reflect the actual number of patients achieved CR/CRp in the model.
- Patients who did not receive the second cycle of induction therapy in the second cycle of the model were considered equivalent to those patients off-treatment for HRQoL purposes. Those patients did not have any costs associated with that cycle. The ERG applied the cost associated with the off-treatment health state to these patients instead.
- Estimation of the proportion of refractory patients receiving salvage therapy-these patients were double adjusted. ERG corrected this so that all refractory patients receiving the first cycle of salvage therapy also received the subsequent cycles of salvage therapy.

ERG's amendments to company's base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)
Company base-case					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£12,251
DA	[redacted]	[redacted]	-	-	-
Company base-case (including ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-

Further scenarios are explored.

ERG's exploratory analyses: courses of treatment

The ERG considers that that the initial treatment costs of the induction and consolidation therapies should be based on the IA response outcomes oppose to IRC.

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Company base-case (including ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-
Scenario: Courses of treatment based on unpooled investigator-assessed (IA) data					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£14,249
DA	[redacted]	[redacted]	-	-	-

	Company modelled values		ERG modelled values	
Proportion of patients	GO+DA group	DA group	GO+DA group	DA group
Induction course 1	[redacted]	[redacted]	[redacted]	[redacted]
Induction course 2	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation course 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation course 2	[redacted]	[redacted]	[redacted]	[redacted]

ERG's exploratory analyses: response rate

- To capture any observed differences, ERG used individual rates of response based on unpooled ALFA-0701 trial data, rather than the pooled rates used in the company's base-case analysis.

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Company base-case (including ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-
Scenario: Rate of response to treatment for individual arms					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£10,526
DA	[redacted]	[redacted]	-	-	-

ICER reduced as a result of the higher response rate for GO+DA patients.

ERG's exploratory analyses: alternative assumptions for HSCT and VOD (1)

- HSCT costs used in the company submission were obtained from a costing study conducted in the Netherlands between 1994 and 1999, since than HSCT costs changed substantially and may not accurately reflect the current costs.
- In the NHS, reference costs of HSCT vary but they also are substantially lower than the unit cost used by the company.
- Overestimating HSCT costs would bias the model in favour of GO+DA as fewer of these patients had an HSCT.
- There is some uncertainty whether the additional inpatient treatment is already captured in the length of stay assumptions.
- The ERG was generally satisfied with the approach to implement the AE-related costs for first-line therapy. However, the ERG considered that patients experiencing VOD would also require inpatient treatment extending beyond the standard stay for treatment with GO due to the associated high mortality risk. There is some uncertainty whether the additional inpatient treatment is already captured in the length of stay assumptions.

ERG's exploratory analyses:
alternative assumptions for HSCT and VOD (2)

	Total costs	Total QALYs	Inc costs	Incr QALYs	ICER
Company base-case (including ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-
Scenario: Alternative HSCT costs					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£16,003
DA	[redacted]	[redacted]	-	-	-
Scenario: Exclusion of additional GVHD costs					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£14,020
DA	[redacted]	[redacted]	-	-	-
Scenario: Exclusion of VOD events in the DA alone group					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,704
DA	[redacted]	[redacted]	-	-	-
Scenario: Inclusion of hospital costs for the treatment of VOD					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,733
DA	[redacted]	[redacted]	-	-	-

ERG's exploratory analyses:
alternative values for functionally cured patients

- The ERG considered the assumption that patients who are functionally cured, experience the same HRQoL as the general population, as not sufficiently justified.
- ERG explored a scenario where functionally cured patients would have lower quality of life than that of the general population.

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Company base-case (with ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-
Scenario: Alternative utility values for functionally cured patients					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,878
DA	[redacted]	[redacted]	-	-	-
Scenario: Alternative utility values for functionally cured patients, adjusted for aging					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£15,279
DA	[redacted]	[redacted]	-	-	-

Both scenarios were associated with lower QALYs and higher ICERs.

ERG's exploratory analyses:
alternative hazard ratio to model excess mortality

The ERG considers that a further adjustment appears appropriate, such that the mortality rate is set equal to the general population mortality rate in instances when the observed mortality rate is reported to be lower than the general population.

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Company base-case (with ERG corrections)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£13,561
DA	[redacted]	[redacted]	-	-	-
Scenario: ERG-estimated HR for long-term survival					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£14,337
DA	[redacted]	[redacted]	-	-	-

ERG's alternative base-case

ERG's changes	ICER
Company base-case	£12,251
Including ERG correct minor calculation errors	£13,561
Number of induction and consolidation therapy (from ALFA-0701 trial)	£14,249
Arm-specific rate of response to treatment	£10,526
The initial cost of HSCT estimated from NHS Reference Costs;	£16,003
Removal of VOD events in the DA treatment group;	£13,704
Exclusion of GVHD-specific costs	£14,020
Inclusion of hospital costs for the treatment of VOD	£13,733
Quality of life in functionally cured patients based on the utility value for off-treatment CR patients, and further adjusted for age	£15,279
Long-term mortality in functionally cured patients adjusted for excess mortality using the ERG-calculated hazard ratio	£14,337
ERG's alternative base-case analysis (all above changes combined)	
Deterministic results	£16,910
Probabilistic results (preferred by ERG)	£17,956

Company's subgroup analyses (1)

Company's rationale for including unknown cytogenetics group:

- According to UK clinical expert opinion less than 10% of patients with de novo AML in the UK present with unknown cytogenetics (in line with the 9.2% included in ALFA-0701).
- An unknown classification may be a consequence of inadequate specimens or non-dividing cells making cytogenetic risk classification impossible. Depending on the severity of symptoms patients may need to be treated immediately rather than waiting for further confirmatory tests therefore it was appropriate to include these patients in the base-case population.

ERG's comments:

- ERG agreed with exclusion of patients with known unfavourable cytogenetics, but believes the heterogeneity in the subgroup of patients with unknown cytogenetics and within the intermediate population was not sufficiently addressed.
- The heterogeneity within the base-case population may have implications concerning the difference in the cure fraction for further subgroups within the overall population.

Company's subgroup analyses (2)

Favourable and intermediate patients (excluding unknown)							
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intermediate patients (excluding unknown and favourable)							
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Removing patients with favourable cytogenetics reduced the estimated statistical cure rates for OS(CR) and RFS in the GO arm.
- Patients with favourable cytogenetics are expected to have better outcomes when treated with GO than those with intermediate cytogenetics.

ERG's additional comments: Subgroups based on cytogenetic and molecular results

Issues with subgroup analysis
The inclusion of patients with unknown cytogenetic results are not fully justified and the differences in the findings between the ALFA-0701 trial and the IPD meta-analysis for this specific subgroup are not sufficiently explained.
The intermediate population is the largest subgroup in the ALFA-0701 trial. The potential impact of heterogeneity between the results of this subgroup and other subgroups included within the base-case population was not sufficiently explored.
The ERG noted the heterogeneity within the intermediate group with regards underlying genetic biomarkers, indicating potential variability in outcomes between individual patients which might be explained by additional molecular testing and further risk-stratification

ERG's exploratory analysis: subgroups by cytogenetic and molecular results (1)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Populations considered by company					
Base-case (Favourable, intermediate and unknown)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£16,910
DA	[redacted]	[redacted]	-	-	-
All patients					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£25,941
DA	[redacted]	[redacted]	-	-	-
Additional cytogenetic subgroups (ERG's exploratory analysis)					
Favourable and intermediate					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£24,581
DA	[redacted]	[redacted]	-	-	-
Intermediate					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£31,709
DA	[redacted]	[redacted]	-	-	-

ERG's exploratory analysis: subgroups by cytogenetic and molecular results (2)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Additional cytogenetic and molecular subgroup (ERG's exploratory analysis)					
Favourable and intermediate-1					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£17,614
DA	[redacted]	[redacted]	-	-	-
Intermediate-1 only					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	£16,343
DA	[redacted]	[redacted]			

These findings can only be considered indicative due to data limitations. Uncertainties remain concerning the practicality and feasibility of introducing additional risk stratification within routine clinical practice.

Innovation and equality

- Company considers gemtuzumab ozogamicin to be innovative:
  - Gemtuzumab ozogamicin targets AML and in combination with DA is able to extend the duration of remission.
  - Gemtuzumab ozogamicin as an add-on to DA therefore represents a step-change in the management of adult patients with de novo AML.
  - The clinical benefits of adding gemtuzumab ozogamicin to DA are particularly apparent in patients with favourable/intermediate cytogenetics profile, but not in patients with unfavourable cytogenetics profile.
  - Gemtuzumab ozogamicin is able to directly target CD33-positive AML blasts in order to induce death of leukaemic cells.
  - Gemtuzumab ozogamicin reduces relapses in patients which can impact on patients' HRQoL, and therefore reduces associated increased costs owing to the need for hospitalization and chemotherapy to induce a second remission.
- No issues equality issues raised during scoping or company submission/ patient professional statements

Key issues – cost effectiveness (1)

- Is the company's model appropriate for decision making given its complexity?
- Is the absence of an explicit structural link between relapse and HSCT appropriate?
- Should the initial treatment costs of the induction and consolidation therapies be based on the IA response outcomes or on an adjustment of the IRC response outcomes as proposed by the company?
- Is it appropriate to pool response data?
- What is the most appropriate HR for long-term morbidity and survival for functionally cured patients?
- Is it appropriate to assume that functionally cured patients experience the same HRQoL as the general population?
- Are the costs for HSCT included in the company's model appropriate?
- Is it appropriate to include patients with VOD in the DA treatment arm in the model?
- Has the additional inpatient treatment costs associated with VOD been adequately captured in the company's model?

Key issues - cost effectiveness and other (2)

Cost effectiveness

- What are the implications of the heterogeneity in the subgroup of patients with unknown cytogenetics and within the intermediate population on the most plausible ICER?
- What is the most plausible ICER?

Other

- Is gentuzumab ozogamicin an innovative treatment?
- Are there any equality issues?