NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Pfizer (company)
   - Leukaemia Care
   - NCRI-ACP-RCP
   - NHS England
   - Novartis Pharmaceuticals UK

   The Department of Health and Social Care submitted a "no comment" response

   There were no comments received from experts

   There were no comments received through the NICE website

3. **Company appendix of new evidence –** submitted by Pfizer

4. **Evidence Review Group critique of company appendix –** provided by Centre for Reviews and Dissemination and Centre for Health Economics – York

July 2018

5. **Company new evidence submission** – submitted by Pfizer

6. **Evidence Review Group Critique of company new evidence submission** – provided by Centre for Reviews and Dissemination and Centre for Health Economics – York

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

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the

submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	NCRI-ACP-RCP	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.	Comment noted. No action required.
2	Consultee	NCRI-ACP-RCP	We feel that this recommendation is unfeasible in clinical practice. For the majority of newly-diagnosed AML patients who are considered suitable for intensive chemotherapy, the cytogenetic result is not currently known prior to starting treatment and will only become available (in current standard UK laboratory set-up) by day 7-14. With GO being scheduled on days 1, 4 and 7 of treatment cycle 1, this will not permit the use of GO with cycle 1 in the setting where a patient is subsequently found to have a favourable karyotype (or indeed in the small minority of patients where cytogenetic analysis has been attempted but is unsuccessful). In this recommendation the very patients that NICE favours receiving GO i.e. with favourable risk disease will not be able to receive it in course 1 where all the evidence shows that it has the most benefit.	Comment noted. The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, and agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics should be taken into account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy). The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and

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				they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.
3	Consultee	NCRI-ACP-RCP	Extensive RCT data has demonstrated benefit from addition of GO to intensive chemotherapy, not only in the patients with favourable cytogenetics, but also in the larger group of patients with normal karyotype (or other intermediate risk abnormalities) – Alfa study, UK AML15 and 16, meta-analysed in >3000 patients by Hills et al. On the basis of these data we strongly advocate further consideration to incorporation of frontline GO for all patients apart from those who are known in advance to have an adverse risk karyotype. In fact a major group to benefit in the intermediate risk category were those with a FLT3 ITD where the HR for survival was 0.3. This group will not benefit in this recommendation	Comment noted. The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, and agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics should be taken into account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy). The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if: they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.

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4	Consultee	NCRI-ACP-RCP	Cytogenetic analysis is only unsuccessful in a small proportion of AML cases – these cases form a completely unselected (seemingly 'random') group of patients with no correlations to defined biological/genetic aspects of AML or established risk groups. Given the wealth of clinical evidence to support addition of GO to intensive chemotherapy in defined biological subgroups of AML patients (see point 2) we consider it disappointing and disheartening, in the setting of extensive, meticulously conducted international clinical research that the proposed access to GO be directed to this seemingly arbitrary group of patients, based on unplanned subgroup analysis.	Comment noted. The committee discussed the proportion of patients for whom result from the analysis were unsuccessful in determining cytogenetic status and agreed that based on the clinical expert opinion such group would not be re-tested but they would generally receive the same treatment as those with favourable or intermediate cytogenetics. No change to the FAD, (see FAD section 3.5).
5	Consultee	NCRI-ACP-RCP	We think that the Committee has not taken due attention to the standard care for patients presenting with AML The diagnosis can be made on bone marrow morphology and immunophenotyping within a few hours. Cytogenetic samples will be sent to the laboratory but results will take 7-14 plus days to be reported. In contrast for a significant proportion of patients the initiation of chemotherapy is urgent, often the same day as presentation or within 24 hours of diagnosis. This is particularly the case in high white cell count AML In the majority of other cases treatment is usually started within 24-48 hours. These patients are usually neutropenic at diagnosis and it would be detrimental and unsafe to delay therapy unnecessarily as this would only prolong the period of time that the patient is at risk of sepsis. To wait for cytogenetic results when the patient is ready to start chemotherapy would be against current practice and potentially put patient safety at risk There are exceptions to this for example patients with low WCC secondary AML with previous MDS may present with a 'grumbling' type of AML. In these cases treatment can be delayed without putting the patient at risk. This is the type of AML that is most likely to have adverse risk cytogenetics and would not be a Mylotarg candidate anyway.	Comment noted**.** The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, and agreed It agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics should be taken to account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy). The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if: they start induction therapy when either the test confirms that the disease has

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				favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.
6	Commentator	Novartis Pharmaceuticals UK Ltd	We are concerned that there is no clear definition of favourable cytogenetics presented within the ACD, while the recommendation (section 1.1) is reliant upon patients having favourable cytogenetics. We would ask that the definition of favourable cytogenetics, as per ELN guidelines, is clearly presented in the appraisal documentation.	Comment noted. The committee considered the favourable, intermediate, unknown and unfavourable cytogenetic profile groups. See FAD section 3.3. The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if: they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD section 1.
7	Commentators	Novartis Pharmaceuticals UK Ltd	**Factual inaccuracy** The following sentence in section 3.11, page 10 appears to contain a factual inaccuracy "*For patients in the favourable or intermediate cytogenetic group, overall survival increased from 38.6 months to 26.0 months (HR 0.747, 95% CI 0.511 to 1.091, p=0.1288).*" The correct wording would be For patients in the favourable or intermediate cytogenetic group, overall survival increased from 26.0 months to 38.6 months (HR 0.747, 95% CI 0.511 to 1.091, p=0.1288). The following sentence in section 3.11, page 10 appears to contain a factual inaccuracy "*For patients who disease had unfavourable cytogenetics, overall survival decreased from 3.14 months to 12.0 months (HR 1.553, CI 0.878 to 2.748, p=0.1267).*" The correct wording would be	Comment noted. The FAD has been amended accordingly. See FAD section 3.10.

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			For patients who disease had unfavourable cytogenetics, overall survival decreased from months 12.0 to 3.14 months (HR 1.553, CI 0.878 to 2.748, p=0.1267).	
8	Others	NHS England	NICE has issued an optimised recommendation for gemtuzumab ozogamicin in combination with daunorubicin and cytarabine as an option for treating newly diagnosed de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over and only if the disease has favourable cytogenetics or in those patients in whom the cytogenetic analysis was unsuccessful. In terms of receiving successful results from testing of cytogenetics, of the approx. 95% of testing that come back with a result (around 5% have unsuccessful testing) NHS England understands that approximately 20% of AML patients have favourable cytogenetics, 60% have intermediate cytogenetics and 20% have unfavourable cytogenetics. NHS England has received consistent expert clinical advice that the first cycle of induction chemotherapy is the most important cycle of chemotherapy and as a consequence requires recommendations for gemtuzumab ozogamicin to be incorporated into the 1st cycle of treatment. NHS England is aware that cytogenetic analyses can take up to 1-2 weeks to be reported. NHS England understands that the majority of patients with AML have to start their chemotherapy on an urgent basis and therefore cannot wait until the results of the cytogenetic analysis are known. This is because such patients are at high risk of dying from the disease and its complications (especially because of infection). NHS England has to implement NICE recommendations in a practical and cost effective way, which both treats the patients which are within the recommended group and at the same time neither prejudices patient safety and outcomes nor cost effectiveness. NHS England regards the current NICE optimised recommendation as being impossible to implement safely and in a cost effective way for the majority of patients as these have to start treatment without waiting for	Comments noted**.** The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, It agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics should be taken to account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy. The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.

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			the results of cytogenetic analysis. Only for a minority of patients, who can safely wait for cytogenetic results, NICE's optimised recommendation can be implemented in a cost effective way without compromising patient outcomes. The only safe way to ensure patients with favourable or unsuccessful cytogenetics receive gemtuzumab ozogamicin would be for all patients who require urgent chemotherapy to be treated with gemtuzumab ozogamicin in the 1st cycle and only to continue with gemtuzumab ozogamicin after this 1st cycle in those patients with favourable or unsuccessful cytogenetics. This would mean cost ineffective use of gemtuzumab ozogamicin in 80% of such patients. The only safe way to ensure patients with unfavourable, intermediate or unsuccessful cytogenetics receive gemtuzumab ozogamicin would be for all patients who require urgent chemotherapy to be treated with gemtuzumab ozogamicin in the 1st cycle and only to continue with gemtuzumab ozogamicin after this 1st cycle in those patients with favourable, intermediate or unsuccessful cytogenetics. This would mean cost ineffective use of gemtuzumab ozogamicin in 20% of such patients. Whichever cytogenetic risk groups are recommended for treatment with gemtuzumab ozogamicin, NICE must examine the cost effectiveness of how any gemtuzumab ozogamicin recommendation can be implemented in practice in a way which treats all the patients for whom gemtuzumab ozogamicin is recommended in a safe manner which in turn recognises the practical realities of optimally treating AML and mitigates the high risk of dying from the disease and its complications	
9	Patient and Professional	Leukaemia Care	We are pleased to see that the committee has recommended the use of gemtuzumab ozogamicin for untreated AML, given the increased clinical benefit that this treatment has for patients in combination with daunorubicin and cytarabine. It has the potential to be a lifesaving treatment option for AML patients who currently have a relatively poor survival rate, with little improvements over the last few decades. However, it is disappointing to see that the recommendation has been	Comments noted. The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, and agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics should be taken to account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin

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			restricted to patients with favourable, or unknown cytogenetic results (because cytogenetic analysis was unsuccessful). We would like to see the recommendation broadened to include patients with intermediate-risk AML and those with unknown cytogenetic results (for whatever reason). Evidence suggests that 5-year survival for patients with intermediate risk cytogenetics is as low as 24% (1). The restricted recommendation of gemtuzumab ozogamicin means that these patients with a high unmet need will be unable to access a treatment that could potentially enable them to live longer without relapse. The intermediate risk group could account for up to 60% of all AML cases (2), meaning that over 1,800 of the 3,100 patients diagnosed with AML each year (3) will be ineligible gemtuzumab ozogamicin. The ALFA-0701 trial demonstrated that treatment is clearly beneficial in this group and therefore, it is a shame to see that the majority of AML patients could be excluded from accessing it. (1) John C. Byrd et al.. "Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461)." *Blood* 100, no. 13 (2002): 4325-4336. Accessed June 06, 2018. doi: 10.1182/blood-2002-03-0772. (2) Veronika Rockova et al.. "Risk stratification of intermediate-risk acute myeloid leukemia: integrative analysis of a multitude of gene mutation and gene expression markers." *Blood* 118, no. 4 (2011): 1069-1076. Accessed June 06, 2018. doi: 10.1182/blood-2011-02-334748. (3) CRUK Incidence Data: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml#heading-Zero	induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy. The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful) or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.
10	Patient and Professional	Leukaemia Care	Acute myeloid leukaemia (AML) is a rapidly progressing and often fatal condition. 53% of patients will have been diagnosed via emergency presentation, compared to a cancer average of 22% (4). In this setting, patients have extremely poor prognosis and there is an urgent need to	Comment noted. The committee acknowledged the importance of being able to start treatment before cytogenetic test results become available, and agreed that including the costs incurred in patients who start induction treatment while waiting for cytogenetic

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			rapidly begin treatment. In a Leukaemia Care survey of 373 AML patients, we found that 32% of AML patients started treatment on the same day that they were given their diagnosis and a further 47% started treatment within a week of receiving their diagnosis (5). As such, we are concerned by the requirement for cytogenetic test results before the start of treatment, which could potentially delay the start of treatment. Additionally, this may limit the usage of gemtuzumab ozogamicin to centres with the capability to quickly turn around test results. We would request that the recommendation be amended to include all patients with unknown cytogenetics (not just those where the cytogenetic analysis was unsuccessful). This would allow gemtuzumab ozogamicin to be utilised upfront (without a requirement to wait for cytogenetic test results) and discontinued in patients with adverse-risk cytogenetics (if deemed clinically appropriate to do so). (4) NCIN, Routes to Diagnosis 2006-2015 http://www.ncin.org.uk/publications/routes_to_diagnosis (5) Living with Leukaemia Report - http://www.leukaemiacare.org.uk/living-with-leukaemia	results and who were later found to have unfavourable cytogenetics should be taken to account in its decision making. The committee also agreed that in clinical practice, patients would have a gemtuzumab ozogamicin induction therapy course while waiting for their cytogenetic results. It therefore agreed a stopping rule; that gemtuzumab ozogamicin should only be continued after induction therapy (i.e. the start of consolidation therapy) in people whose disease did not have unfavourable cytogenetics (that is, people whose disease has favourable, intermediate or unknown cytogenetics [because the cytogenetic analysis is unsuccessful]). The committee considered the revised cost effectiveness analyses provided by the company in response to consultation, which included induction treatment before cytogenetic test results become available, and the stopping rule for people with unfavourable cytogenetics after induction treatment (and before consolidation therapy. The committee has now recommended gemtuzumab ozogamicin in people 15 years and over, only if they start induction therapy when either the test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is because the test was unsuccessful), or when their cytogenetic test results are not yet available and they start consolidation therapy when their test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful). See FAD sections 1, 3.4, 3.16, 3.21-3.24 and 3.28.

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: **5pm Monday 18 June 2018** return via NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for gemtuzumab ozogamicin as an option for treating de novo acute myeloid leukaemia (AML) patients. Pfizer welcomes the committee's views of recognising the efficacious nature, and tolerability, of gemtuzumab ozogamicin.
2	Pfizer believes that compelling evidence has been presented in the submission which would support a positive recommendation inclusive of patients with intermediate cytogenetics profile. We are concerned that the draft recommendation excludes patients with intermediate cytogenetics profile which accounts for approximately 60% of the patient population. In clinical practice in the UK, unless patients are known to have unfavourable cytogenetics' profile, patients would receive treatment. Hence, Pfizer submitted a case in which the population specified in the decision problem included all AML patients with favourable or intermediate or unknown cytogenetic status, i.e. patients not known to have unfavourable cytogenetics profile. For this population gemtuzumab ozogamicin is a highly cost-effective option for treating de novo AML patients; the committee's most plausible ICER is £16,910 per QALY gained. Whilst we acknowledge clinicians have said that the intermediate 1 and 2 classification is outdated, we would like to highlight that intermediate-1 subgroup accounts for two thirds of the total patients expected to be treated in clinical practice and it has been deemed as cost-effective. Therefore, we would like the committee to show more flexibility in its decision making, as we are concerned that the intermediate 2 patient subgroup, which has been deemed as being not cost-effective, is driving the

	overall ICER for this clinically important subgroup.
3	It must be noted that, intensive treatment for AML patients is essentially unchanged in 40 years and the unmet clinical need remains substantial for all patients, including those with unknown and intermediate cytogenetics' profile. Gemtuzumab ozogamicin is a "step change" in the management of AML patients; it is the first drug that has consistently shown survival benefit in AML when added to standard induction chemotherapy. Without access to this innovative medicine patients will continue to experience poor clinical outcomes. We continue to believe that we have presented a compelling case to allow access to gemtuzumab ozogamicin for all patients in England and Wales.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	[redacted] Campaigns and Advocacy Director

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are pleased to see that the committee has recommended the use of gemtuzumab ozogamicin for untreated AML, given the increased clinical benefit that this treatment has for patients in combination with daunorubicin and cytarabine. It has the potential to be a lifesaving treatment option for AML patients who currently have a relatively poor survival rate, with little improvements over the last few decades. However, it is disappointing to see that the recommendation has been restricted to patients with favourable, or unknown cytogenetic results (because cytogenetic analysis was unsuccessful). We would like to see the recommendation broadened to include patients with intermediate-risk AML and those with unknown cytogenetic results (for whatever reason). Evidence suggests that 5-year survival for patients with intermediate risk cytogenetics is as low as 24% (1). The restricted recommendation of gemtuzumab ozogamicin means that these patients with a high unmet need will be unable to access a treatment that could potentially enable them to live longer without relapse. The intermediate risk group could account for up to 60% of all AML cases (2), meaning that over 1,800 of the 3,100 patients diagnosed with AML each year (3) will be ineligible gemtuzumab ozogamicin. The ALFA-0701 trial demonstrated that treatment is clearly beneficial in this group and therefore, it is a shame to see that the majority of AML patients could be excluded from accessing it.

Please return via **NICE Docs**

	(1) John C. Byrd et al.. "Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461)." *Blood* 100, no. 13 (2002): 4325-4336. Accessed June 06, 2018. doi: 10.1182/blood-2002-03-0772. (2) Veronika Rockova et al.. "Risk stratification of intermediate-risk acute myeloid leukemia: integrative analysis of a multitude of gene mutation and gene expression markers." *Blood* 118, no. 4 (2011): 1069-1076. Accessed June 06, 2018. doi: 10.1182/blood-2011-02-334748. (3) CRUK Incidence Data: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml#heading-Zero
2	Acute myeloid leukaemia (AML) is a rapidly progressing and often fatal condition. 53% of patients will have been diagnosed via emergency presentation, compared to a cancer average of 22% (4). In this setting, patients have extremely poor prognosis and there is an urgent need to rapidly begin treatment. In a Leukaemia Care survey of 373 AML patients, we found that 32% of AML patients started treatment on the same day that they were given their diagnosis and a further 47% started treatment within a week of receiving their diagnosis (5). As such, we are concerned by the requirement for cytogenetic test results before the start of treatment, which could potentially delay the start of treatment. Additionally, this may limit the usage of gemtuzumab ozogamicin to centres with the capability to quickly turn around test results. We would request that the recommendation be amended to include all patients with unknown cytogenetics (not just those where the cytogenetic analysis was unsuccessful). This would allow gemtuzumab ozogamicin to be utilised upfront (without a requirement to wait for cytogenetic test results) and discontinued in patients with adverse-risk cytogenetics (if deemed clinically appropriate to do so). (4) NCIN, Routes to Diagnosis 2006-2015 http://www.ncin.org.uk/publications/routes_to_diagnosis (5) Living with Leukaemia Report - http://www.leukaemiacare.org.uk/living-with-leukaemia

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], RCP registrar

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We feel that this recommendation is unfeasible in clinical practice. For the majority of newly-diagnosed AML patients who are considered suitable for intensive chemotherapy, the cytogenetic result is not currently known prior to starting treatment and will only become available (in current standard UK laboratory set-up) by day 7-14. With GO being scheduled on days 1, 4 and 7 of treatment cycle 1, this will not permit the use of GO with cycle 1 in the setting where a patient is subsequently found to have a favourable karyotype (or indeed in the small minority of patients where cytogenetic analysis has been attempted but is unsuccessful). In this recommendation the very patients that NICE favours receiving GO ie, with favourable risk disease will not be able to receive it in course 1 where all the evidence shows that it has the most benefit.
2	Extensive RCT data has demonstrated benefit from addition of GO to intensive chemotherapy, not only in the patients with favourable cytogenetics, but also in the larger group of patients with normal karyotype (or other intermediate risk abnormalities) – Alfa study, UK AML15 and 16, meta-analysed in >3000 patients by Hills et al. On the basis of these data we strongly advocate further consideration to incorporation of frontline GO for all patients apart from those who are known in advance to have an adverse risk karyotype. In fact a major group to benefit in the intermediate risk category were those with a FLT3 ITD where the HR for survival was 0.3. This group will not benefit in this recommendation
3	Cytogenetic analysis is only unsuccessful in a small proportion of AML cases – these cases form a

	completely unselected (seemingly 'random') group of patients with no correlations to defined biological/genetic aspects of AML or established risk groups. Given the wealth of clinical evidence to support addition of GO to intensive chemotherapy in defined biological subgroups of AML patients (see point 2) we consider it disappointing and disheartening, in the setting of extensive, meticulously conducted international clinical research that the proposed access to GO be directed to this seemingly arbitrary group of patients, based on unplanned subgroup analysis.
4	We think that the Committee has not taken due attention to the standard care for patients presenting with AML The diagnosis can be made on bone marrow morphology and immunophenotyping within a few hours. Cytogenetic samples will be sent to the laboratory but results will take 7-14 plus days to be reported. In contrast for a significant proportion of patients the initiation of chemotherapy is urgent, often the same day as presentation or within 24 hours of diagnosis. This is particularly the case in high white cell count AML In the majority of other cases treatment is usually started within 24-48 hours. These patients are usually neutropenic at diagnosis and it would be detrimental and unsafe to delay therapy unnecessarily as this would only prolong the period of time that the patient is at risk of sepsis. To wait for cytogenetic results when the patient is ready to start chemotherapy would be against current practice and potentially put patient safety at risk There are exceptions to this for example patients with low WCC secondary AML with previous MDS may present with a 'grumbling' type of AML. In these cases treatment can be delayed without putting the patient at risk. This is the type of AML that is most likely to have adverse risk cytogenetics and would not be a Mylotarg candidate anyway.

Insert extra rows as needed

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: **5pm Monday 18 June 2018** return via NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Professor Peter Clark

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	NICE has issued an optimised recommendation for gemtuzumab ozogamicin in combination with daunorubicin and cytarabine as an option for treating newly diagnosed de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over and only if the disease has favourable cytogenetics or in those patients in whom the cytogenetic analysis was unsuccessful. In terms of receiving successful results from testing of cytogenetics, of the approx. 95% of testing that come back with a result (around 5% have unsuccessful testing) NHS England understands that approximately 20% of AML patients have favourable cytogenetics, 60% have intermediate cytogenetics and 20% have unfavourable cytogenetics. NHS England has received consistent expert clinical advice that the first cycle of induction chemotherapy is the most important cycle of chemotherapy and as a consequence requires recommendations for gemtuzumab ozogamicin to be incorporated into the 1st cycle of treatment. NHS England is aware that cytogenetic analyses can take up to 1-2 weeks to be reported. NHS England understands that the majority of patients with AML have to start their chemotherapy on an urgent basis and therefore cannot wait until the results of the cytogenetic analysis are known. This is because such patients are at high risk of dying from the disease and its complications (especially because of infection). NHS England has to implement NICE recommendations in a practical and cost effective way, which both treats the patients which are within the recommended group and at the same time neither prejudices patient safety and outcomes nor cost effectiveness.

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	NHS England regards the current NICE optimised recommendation as being impossible to implement safely and in a cost effective way for the majority of patients as these have to start treatment without waiting for the results of cytogenetic analysis. Only for a minority of patients, who can safely wait for cytogenetic results, NICE's optimised recommendation can be implemented in a cost effective way without compromising patient outcomes. The only safe way to ensure patients with favourable or unsuccessful cytogenetics receive gemtuzumab ozogamicin would be for all patients who require urgent chemotherapy to be treated with gemtuzumab ozogamicin in the 1st cycle and only to continue with gemtuzumab ozogamicin after this 1st cycle in those patients with favourable or unsuccessful cytogenetics. This would mean cost ineffective use of gemtuzumab ozogamicin in 80% of such patients. The only safe way to ensure patients with unfavourable, intermediate or unsuccessful cytogenetics receive gemtuzumab ozogamicin would be for all patients who require urgent chemotherapy to be treated with gemtuzumab ozogamicin in the 1st cycle and only to continue with gemtuzumab ozogamicin after this 1st cycle in those patients with favourable, intermediate or unsuccessful cytogenetics. This would mean cost ineffective use of gemtuzumab ozogamicin in 20% of such patients. Whichever cytogenetic risk groups are recommended for treatment with gemtuzumab ozogamicin, NICE must examine the cost effectiveness of how any gemtuzumab ozogamicin recommendation can be implemented in practice in a way which treats all the patients for whom gemtuzumab ozogamicin is recommended in a safe manner which in turn recognises the practical realities of optimally treating AML and mitigates the high risk of dying from the disease and its complications.

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: **5pm Monday 18 June 2018** return via NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Novartis Pharmaceuticals UK Ltd**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that there is no clear definition of favourable cytogenetics presented within the ACD, while the recommendation (section 1.1) is reliant upon patients having favourable cytogenetics. We would ask that the definition of favourable cytogenetics, as per ELN guidelines, is clearly presented in the appraisal documentation.
2	**Factual inaccuracy** The following sentence in section 3.11, page 10 appears to contain a factual inaccuracy "*For patients in the favourable or intermediate cytogenetic group, overall survival increased from 38.6 months to 26.0 months (HR 0.747, 95% CI 0.511 to 1.091, p=0.1288).*" The correct wording would be For patients in the favourable or intermediate cytogenetic group, overall survival increased from 26.0 months to 38.6 months (HR 0.747, 95% CI 0.511 to 1.091, p=0.1288). The following sentence in section 3.11, page 10 appears to contain a factual inaccuracy "*For patients who disease had unfavourable cytogenetics, overall survival decreased from 3.14 months to 12.0 months (HR 1.553, CI 0.878 to 2.748, p=0.1267).*" The correct wording would be For patients who disease had unfavourable cytogenetics, overall survival decreased from months 12.0 to 3.14 months (HR 1.553, CI 0.878 to 2.748, p=0.1267).

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Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: **5pm Monday 18 June 2018** return via NICE DOCS

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ID982 Appraisal of gemtuzumab ozogamicin
18th June 2018

Dear Professor O'Brien,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for gemtuzumab ozogamicin as an option for treating de novo acute myeloid leukaemia (AML) patients.

Pfizer welcomes the committee's views of recognising the efficacious nature, and tolerability, of gemtuzumab ozogamicin.

Pfizer believes that compelling evidence has been presented in the submission which would support a positive recommendation inclusive of patients with intermediate cytogenetics profile.

We are concerned that the draft recommendation excludes patients with intermediate cytogenetics profile which accounts for approximately 60% of the patient population. In clinical practice in the UK, unless patients are known to have unfavourable cytogenetics' profile, patients would receive treatment. Hence, Pfizer submitted a case in which the population specified in the decision problem included all AML patients with favourable or intermediate or unknown cytogenetic status, i.e. patients not known to have unfavourable cytogenetics profile. For this population gemtuzumab ozogamicin is a highly cost-effective option for treating de novo AML patients; the committee's most plausible ICER is £16,910 per QALY gained.

Whilst we acknowledge clinicians have said that the intermediate 1 and 2 classification is outdated, we would like to highlight that intermediate-1 subgroup accounts for two thirds of the total patients expected to be treated in clinical practice and it has been deemed as cost-effective. Therefore, we would like the committee to show more flexibility in its decision making, as we are concerned that the intermediate 2 patient subgroup, which has been deemed as being not cost-effective, is driving the overall ICER for this clinically important subgroup.

In response to the ACD, Pfizer performed further adjustments to the committee set of preferred economic estimates which included: adjustments to the utility values for the functionally cured patients, VOD related impatient days and update to mixture cure model parameters. We noted that some of the ERG adjustments were not clinically plausible. The cumulative impact of these changes decrease the ICER for this clinically important intermediate subgroup to £28,813 per QALY gained.

We have also explored price sensitivity analyses to the intermediate cytogenetics' profile subgroup based on the committee's preferred set of assumptions which demonstrate that a net discount of [redacted] would be required in order to demonstrate cost-effectiveness below the £30,000 per QALY gained threshold. Such a discount would be applied to all patients in the Pfizer base-case population. Pfizer is very keen to find a timely solution to avoid lengthy delays in access to this significant group of patients.

The committee asked Pfizer to undertake an analysis in which a stopping rule for treatment with gemtuzumab ozogamicin is applied for patients who are still waiting for the results of cytogenetic testing. It was not possible to model the clinical impact of such a stopping rule based on the available evidence from the ALFA trial. However, we did explore a scenario analysis whereby only the cost-offset associated with receiving less courses of treatment is applied and unsurprisingly the cost-effectiveness estimates improved.

It must be noted that, intensive treatment for AML patients is essentially unchanged in 40 years and the unmet clinical need remains substantial for all patients, including those with unknown and

intermediate cytogenetics' profile. Gemtuzumab ozogamicin is a "step change" in the management of AML patients; it is the first drug that has consistently shown survival benefit in AML when added to standard induction chemotherapy. Without access to this innovative medicine patients will continue to experience poor clinical outcomes. We continue to believe that we have presented a compelling case to allow access to gemtuzumab ozogamicin for all patients in England and Wales.

Yours sincerely,

[redacted]

A. Adjustments to ERG structural changes

A number of proposed corrections and structural changes to the Pfizer submitted model were made by the ERG. These generated cost-effectiveness estimates that were preferred by the NICE committee across all populations considered in this appraisal.

Pfizer has investigated one correction and two structural changes proposed by the ERG as it believes these can impact the committee preferred cost-effectiveness estimates for both populations:

- patients not known to have unfavourable cytogenetics profile (Pfizer base-case);
- patients with intermediate cytogenetics' profile.

These corrections and structural changes included:

- Quality of life in functionally cured patients;
- Hospital inpatient days for VOD;
- Update to mixture cure model (MCM) parameters.

Table 1 summarises the single change and all change ICERs for each of these adjustments. Table 2 summarises the single change and all change ICERs for intermediate patients but under different pricing scenarios. For a full breakdown of results see the appendices (Table 4, Table 5 and Table 6)

Quality of life in functionally cured patients

The committee considered it reasonable to assume that functionally cured patients would have lower quality of life than that of general population, given the assumption that functionally cured patients experience a higher mortality risk than the general population. Whilst Pfizer does not disagree with this assumption, the utility values considered by the ERG in their exploratory scenario are clinically implausible as the utility values associated with patients in remission (0.74) were also applied to that of functionally cured patients.

Consequently, functionally cured patients (i.e. patients who do not experience a relapse event for 5 years), will have lower health-related quality of life (HRQoL) in any given point in time than patients in complete remission. This results in a reduction in HRQoL as a patient moves from complete remission to functionally cured status. This ordering is not clinically plausible as the utility values associated with patients in remission should be lower than those associated to be functionally cured patients.

Pfizer commissioned an independent preference elicitation study (see section B.3.4 of company submission) the results of which preserve this order; in both the TTO and VAS valuation methods the utility for functionally cured patients is significantly higher than for patients in complete remission (23% and 34% higher respectively). Please see in the appendices of this response document for a full breakdown of available utilities (also presented in the appendix of the Pfizer's submission).

Pfizer proposes two alternatives that preserve the appropriate ordering of utilities. The first is a starting value of 0.76, which is the TTO derived utility value for functionally cured patients from the Pfizer utility study. The second is 0.77 and is taken from the same source as the ERG's (TA399 (0.74)) but is based on a different mapping algorithm (Proskorovsky et al, 2014). In each of these scenarios the utility for the complete remission state remains at 0.74.

Both impact the cost-effectiveness estimates. Pfizer's preference is 0.77 because it is better at preserving the required utility ordering in each of the model cycles.

Hospital inpatient days for VOD

Pfizer's analysis included the cost of endoscopic ultrasound examination and a course of defibrotide in the unit cost applied for the incidence of the adverse event VOD (venous occlusive disease). The ERG analysis added the cost of 26.8 inpatient hospital days to this unit cost, in excess of inpatient days associated with first line treatments. The ERG assumed that the excess inpatient days due to VOD would be in line with the duration of the disutility applied for VOD in the model (26.8 days).

This disutility duration was sourced from the NICE submission for inotuzumab ozogamicin (ID893; NICE, 2017) and is the average duration of VOD in the trial associated with that submission (INO-VATE 1022).

However, this is the duration of VOD associated with HSCT, which is not the same as the VOD associated with gemtuzumab ozogamicin treatment. Clinicians validated that the VOD associated with gemtuzumab ozogamicin is of a milder form than that associated with HSCT. This is evidenced by the treatment protocol for VOD in the ALFA trial: 10 mg/kg of defibrotide was administered daily for only 7 days in contrast to more extensive defibrotide use in the treatment of VOD associated with HSCT (e.g. 6.25mg/kg every 6 hours for 21 days). In addition, 26.8 days of hospitalisation is very close to the 28.48 excess bed days associated with severe VOD (under defibrotide treatment) estimated in the NHS guidance "Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant" (NHS England, 2015).

Pfizer believes that 26.8 excess bed days associated with VOD following gemtuzumab ozogamicin is an overestimate. Following receipt of the ACD, Pfizer consulted with clinicians who suggested the range from 14 to 28 days to be more plausible. Applying the mid-point of this range (21 days) lowers the estimated costs in the gemtuzumab ozogamicin +DA arm and consequently the ICERs.

Update to mixture cure model (MCM) parameters

The ERG updated the lifetables (ONS, 2017) in their analyses. MCM estimation involves a weighted average of survival for "uncured" and "cured" patients, whereby the cured group's predicted rate of mortality is based on inputted lifetables during estimation. Therefore, Pfizer re-estimated the base-case MCM curves with background mortality based on the new lifetables and updated the MCM parameters in the model. These corrections changed the cost-effectiveness estimates marginally and decreased the intermediate only ICER.

Summary of Pfizer's adjustments to the ERG analysis

Table 1 - Summary results (ICERs) with Pfizer's adjustments to the ERG analysis

#	Company adjustment	Pfizer base-case population	Patients with intermediate cytogenetics' profile
Single change ICERs:			
1	0.76 (with aging) utility for functionally cured patients	£16,279	£29,923
2	0.77 (with aging) utility for functionally cured patients	£15,960	£29,048
3	21 excess inpatient days for VOD	£16,833	£31,552
4	Updated MCM parameters	£17,006	£31,612
All change ICERs:			
ERG analysis		£16,910	£31,709
Company revised base-case (2+3+4)		**£15,977**	**£28,813**
Company revised base-case (1+3+4)		**£16,296**	**£29,682**
Company revised base-case (2+4)		**£16,050**	**£28,956**

The adjustments made to the ERG structural changes impact the cost-effectiveness estimates and are likely to alter the committee's preliminary decision of not recommending gemtuzumab ozogamicin to patients with intermediate cytogenetics' profile. For this population, the ICER falls below £30,000 per QALY gained (£28,813/QALY).

B. Pricing scenario analysis

We have also undertaken further price sensitivity analyses in the event that no changes are accepted by the Committee to their preferred set of assumptions. Table 2 below also presents the results showing that minimum level of net price discount required in order to demonstrate cost-effectiveness of gemtuzumab ozogamicin for patients within the intermediate cytogenetics' profile subgroup is [redacted] reducing the cost per QALY estimate to [redacted]

Please note that Pfizer would be willing to offer a simple PAS. Whilst the PAS would not be approved by PASLU in time for the second appraisal committee meeting on the 27th of June, conversations with NICE signalled that such a PAS could be considered, at risk, during the second part of the meeting.

Table 2 - Cost-effectiveness estimates for the intermediate cytogenetics' subgroup with PAS

#	Company adjustment	Intermediate only ICER	Intermediate only ICER (with simple [redacted] PAS)
Single change ICERs:			
1	0.76 (with aging) utility for functionally cured patients	£29,923	[redacted]
2	0.77 (with aging) utility for functionally cured patients	£29,048	[redacted]
3	21 excess inpatient days for VOD	£31,552	[redacted]
4	Updated MCM parameters	£31,612	[redacted]
All change ICERs:			
ERG analysis		£31,709	[redacted]
Company revised base-case (2+3+4)		**£28,813**	[redacted]
Company revised base-case (1+3+4)		**£29,682**	[redacted]
Company revised base-case (2+4)		**£28,956**	[redacted]

C. Stopping rule for patients with unknown cytogenetics where the test was not undertaken

The committee requested a cost effectiveness analysis in which patients would receive gemtuzumab ozogamicin while the cytogenetic results are awaited and treatment with gemtuzumab ozogamicin would only be continued in course 2 and beyond in patients whose disease had favourable cytogenetics. The full details of this analysis are presented in the appendix of this response.

Pfizer would like to highlight that, in the cost-effectiveness analysis provided in the submission, virtually all patients receive one course of induction therapy, irrespective of cytogenetic status including those with unknown cytogenetics' profile. At the end of induction therapy, patients are assessed and either respond to treatment, or fail induction therapy (i.e., are refractory) and only those that respond to treatment continue up to two courses of consolidation therapy. Therefore, there is an implicit stopping rule based on treatment response.

The scenario presented here adjusts the proportion of patients who would receive gemtuzumab ozogamicin in each course after a stopping rule is implemented. Unknown cytogenetic patients who do not require urgent care can wait for test results. Unknown cytogenetic patients who must be

treated urgently receive induction 1 and wait for the result of cytogenetic testing; depending on the cytogenetic profile patients may no longer receive consolidation 1 and consolidation 2.

The stopping rule applied to the restricted population of focus in the ACD (favourable and unknown cytogenetics) removed patients classified as having intermediate or adverse cytogenetics. The stopping rule applied to the Pfizer base-case population (favourable, intermediate and unknown cytogenetics) removed patients who are eventually classified as having adverse cytogenetics.

These analyses imply that implementing a stopping rule will decrease costs in the gemtuzumab ozogamicin arm because less gemtuzumab ozogamicin will be used - i.e. a cost offset is applied to go use in each course. As explained in the appendix, there was no data to model how a stopping rule would affect the lifetime relative efficacy of gemtuzumab ozogamicin. However, if it is assumed that patients in which gemtuzumab ozogamicin it is relatively less effective, it may be safe to assume that relative efficacy would not change significantly.

Table 3. Results of stopping rule scenario analyses

Output	**Pfizer base-case population**		**Restricted population**	
	Scenario 1	**Scenario 2**	**Scenario 1**	**Scenario 2**
Induction 1 cost offset	£113	£157	£2,955	£4,116
Consolidation 1 total cost offset	£24	£34	£918	£1,279
Consolidation 2 total cost offset	£24	£34	£918	£1,279
New ICER (ERG base-case)	£16,739	£16,672	N/A	N/A
New ICER (Pfizer adjusted)	£15,815	£15,752	N/A	N/A

In the Pfizer base-case population scenarios, so few patients are affected by the cost offsets associated with the stopping rule (< 1%) that there is very little effect on the ICER (Table 3). It was not possible to compute the cost-effectiveness estimates for the restricted population (favourable + intermediate) because MCM base-case curves (OS(CR) and RFS) cannot be fit to the small number of relevant patients (12 per arm), but the cost-offsets are provided. These cost offsets are more significant because unknown patients constitute a larger proportion of the restricted population and more patients forgo gemtuzumab ozogamicin when the stopping rule is applied in this population.

It is clear that gemtuzumab ozogamicin is highly cost-effective in the restricted population (favourable + unknown) because the ERG intermediate only ICER was £31,709 and adding the remaining favourable and unknown cytogenetics patients decreased the ERG ICER to £16,910. Applying the cost-offset associated with the stopping rule to the restricted population would make this group even more cost-effective.

When assessing the suitability of a stopping rule, considerations about the treatment pathway and practicality of implementing it in clinical practice should also be taken into account. Pfizer has consulted with clinicians and there are doubts about whether such a rule would function as intended in everyday clinical practice; physicians may simply forego the use of GO altogether instead of waiting for the results of cytogenetic testing. Therefore, given that cost-effectiveness in the Pfizer base-case population is not significantly affected by the stopping rule, Pfizer believes that a recommendation for all unknown cytogenetic patients (i.e. without stopping rule) is more appropriate.

APPENDIX

Full results of adjustments to ERG structural changes

The tables below (Table 4, Table 5 and Table 6) present the full QALY and cost results for each of the adjustments described in section A.

Table 4 - Correction of MCM parameters

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Single change ICER
Base-case population					
ERG analysis					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£16,910**
DA	[redacted]	[redacted]	-	-	**-**
Pfizer model scenario: Correction to MCM parameters					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£17,006**
DA	[redacted]	[redacted]	-	-	**-**
Intermediate cytogenetics' profile:					
ERG analysis					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£31,709**
DA	[redacted]	[redacted]	-	-	**-**
Pfizer model scenario: Correction to MCM parameters					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£31,612**
DA	[redacted]	[redacted]	-	-	**-**

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; GO, gemtuzumab ozogamicin; DA, daunorubicin and cytarabine

Based on deterministic analysis

Table 5 - Adjust inclusion of inpatient days for VOD

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Single change ICER
Base-case population:					
ERG analysis (26.8 days)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£16,910**
DA	[redacted]	[redacted]	-	-	**-**
Scenario: adjusted inpatient days (21 days)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£16,833**
DA	[redacted]	[redacted]	-	-	**-**
Intermediate cytogenetics' profile:					
ERG analysis (26.8 days)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£31,709**
DA	[redacted]	[redacted]	-	-	**-**
Scenario: adjusted inpatient days (21 days)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£31,552**
DA	[redacted]	[redacted]	-	-	**-**

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; GO, gemtuzumab ozogamicin; DA, daunorubicin and cytarabine; VOD, venous occlusive disease

Based on deterministic analysis

Table 6 - Utility values in functionally cured patients

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Single change ICER
Pfizer base-case:					
ERG analysis (with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£16,910**
DA	[redacted]	[redacted]	-	-	**-**
Scenario 1: adjusted quality of life (0.76 with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£16,279**
DA	[redacted]	[redacted]	-	-	**-**
Scenario 2: adjusted quality of life (0.77 with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£15,960**
DA	[redacted]	[redacted]	-	-	**-**
Patients with intermediate cytogenetics' profile:					
ERG analysis (with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£31,709**
DA	[redacted]	[redacted]	-	-	**-**
Scenario 1: adjusted quality of life (0.76 with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£29,923**
DA	[redacted]	[redacted]	-	-	**-**
Scenario 2: adjusted quality of life (0.77 with aging)					
GO + DA	[redacted]	[redacted]	[redacted]	[redacted]	**£29,048**
DA	[redacted]	[redacted]	-	-	-

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; GO, gemtuzumab ozogamicin; DA, daunorubicin and cytarabine

Based on deterministic analysis

Stopping rule for patients with unknown cytogenetics

The committee agreed to approve the use of GO in patients whose cytogenetic analysis was unsuccessful, but could not make a recommendation for patients who have unknown cytogenetics because the cytogenetic test results are not available. The ACD requested scenario analyses investigating a stopping rule for the treatment of patients who present with unknown cytogenetic status because of a delay in receiving the results of testing. The analysis was conducted for the following populations:

- Pfizer base-case population: favourable, intermediate and unknown cytogenetics.
- The restricted population (based on recommendation in ACD): favourable and unknown cytogenetics.

In order to implement the stopping rule in full the following two adjustments are required:

- 1st line treatment adjustments: adjustments in the proportion of patients in the relevant courses of the gemtuzumab ozogamicin arm that normally receive gemtuzumab ozogamicin (induction 1, consolidation 1 and consolidation 2) and calculation of appropriate cost offsets.
- Lifetime efficacy adjustments: The deletion of patients in the gemtuzumab ozogamicin arm who would be "netted out" by the stopping rule and subsequent refitting of curves (RFS, OS) or adjustment of curves. Subsequent recalculation of model probabilities relating to relapse, death, Hematopoietic stem cell transplantation and so on.

The scenario analyses reflect the first adjustment. The proportions in the current model who obtain each course of gemtuzumab ozogamicin reflect the proportion in the ALFA trial (and so reflect the ALFA trial protocol). Therefore virtually all patients are treated with induction 1 in the model, irrespective of cytogenetic status and including those with unknown cytogenetics. Treatment with gemtuzumab ozogamicin in consolidation 1 and 2 depended on ALFA protocol and in particular was determined by CR or CRp (and so irrespective of cytogenetic status). These analyses calculate the cost-offset in the arm associated with reduction in gemtuzumab ozogamicin use based on application of the stopping rule.

The second adjustment is not possible with the information available from the ALFA trial. In particular, it is impossible to know which patients to remove or adjust for (and refit curves) before recalculating probabilities because it is not known who from those with unknown cytogenetics in the ALFA data would in real world practice be the following: patients for who there is a delay in cytogenetic testing (instead of test failure); of these patients those who would require urgent treatment (e.g. within 24 hours); and of the remaining who would end up having the required cytogenetic profile for treatment with gemtuzumab ozogamicin.

Method and parameters

These scenario analyses take the proportion of the relevant population that are expected to have unknown cytogenetics and using the parameters in **Error! Reference source not found.** calculate the numbers of these (as a proportion of the total population) who will receive less gemtuzumab ozogamicin based on the following categories:

- Those that are waiting for a test who do not need urgent treatment with gemtuzumab ozogamicin. The proportion of patients who end up not requiring gemtuzumab ozogamicin based on cytogenetics do not receive induction 1, consolidation 1 and consolidation 2.
- Those that are waiting for a test who do need urgent treatment with gemtuzumab ozogamicin. The proportion of patients who end up not requiring gemtuzumab ozogamicin based on cytogenetics receive induction 1 but not consolidation 1 and consolidation 2.

The patients who do not receive gemtuzumab ozogamicin based on cytogenetic status will vary depending on the population. For the Pfizer base-case population (favourable, intermediate,

unknown) analysis, patients with unfavourable cytogenetics will not receive gemtuzumab ozogamicin. For the restricted population (favourable and unknown) analysis, patients with unfavourable or intermediate cytogenetics will not receive gemtuzumab ozogamicin.
For patients to be eligible for consolidation 1 and 2 requires CR or CRp and this is taken into account when calculating the proportion of patients that avoid consolidation 1 and 2. The proportion who forego treatment with gemtuzumab ozogamicin in each of these courses are then multiplied by the average cost of GO treatment in the relevant course. This gives the cost offset - as an average across all patients in the population - and equates to the decrease in gemtuzumab ozogamicin cost because of application of the stopping rule. This cost offset can be used to down-weight course related costs in the model and provide an ICER for the Pfizer base-case population with the stopping rule applied. There is no ICER available for the restricted population (favourable + intermediate) because MCM base-case curves (OS(CR) and RFS) cannot be fit to the small number of relevant patients (12 per arm), but the cost-offsets are provided. A visual representation of the stopping rule is provided in Figure 1.

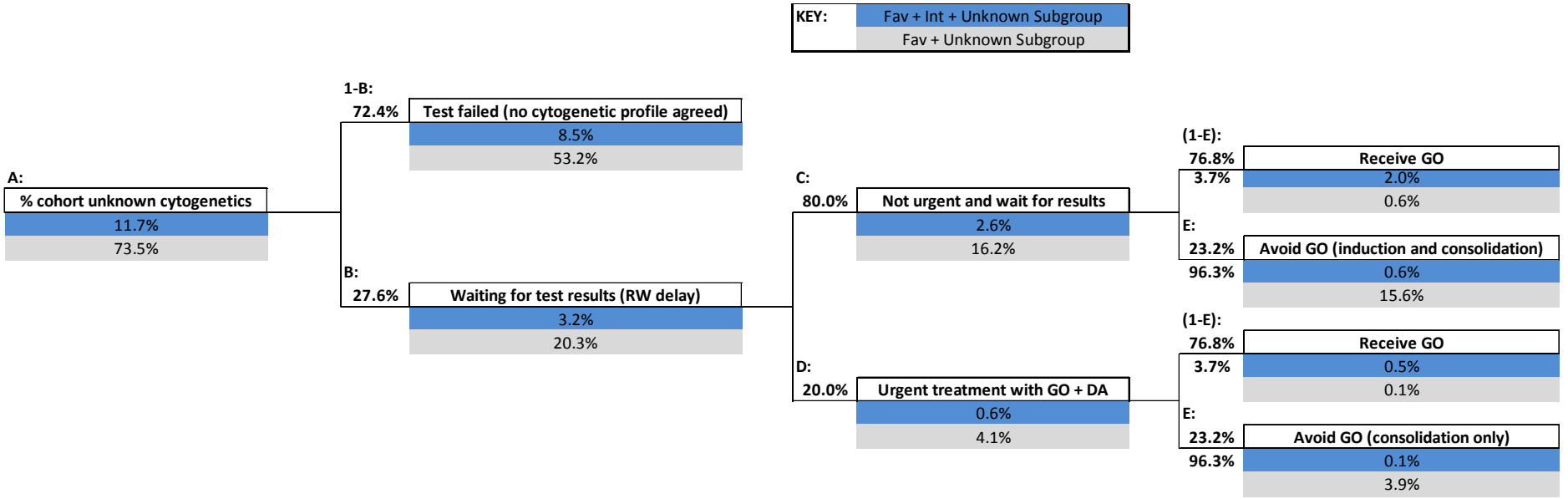
Table 7. Parameters for stopping rule scenario 1

Proportion	Parameters	Pfizer base-case population	Restricted population	Source
A (population specific)	% of model population who have unknown cytogenetics	11.7%	73.5%	ALFA trial. N of unknown cytogenetics/total population
B	% of A who are waiting for results (i.e. test not failed)	27.6%		Castaigne (2012) ALFA trial publication. 21/29 unknown because of test failure, 8/29 not available
C	% of B who do not require urgent treatment	80%		Clinical estimate
D (=1-C)	% of B who do require urgent treatment	20%		Clinical estimate
E (population specific)	% of C and D who do not receive gemtuzumab ozogamicin based on stopping rule	23.2%	96.3%	ALFA trial. N of those with incorrect cytogenetics/total population

There is some uncertainty around the proportion of unknowns because of a delay in receiving results (vs. test failure). In scenario 2, alternative proportions are inputted for parameter B based on a pooled sample of AML 12, 14, 15 and 16 trial patients (Chilton et al, 2017). Of 1,517 patients without a cytogenetic sample, 583 had no sample available (for the remaining 934 the test failed) suggesting B = 38.4%.
Parameters C and D are clinical estimates provided to Pfizer after the ACM. The scenario is relatively insensitive to changes in these proportions because some proportion of both these groups forego gemtuzumab ozogamicin treatment according to the stopping rule. In the ACD it is stated:
"*The committee also recalled that urgent therapy is required if the patient has a very high white blood cell count, a rapidly increasing white blood cell count, evidence of tumour lysis and/or disseminated intravascular coagulation or has life-threatening bleeding or infection* (see section 3.6)."

It is unclear from the information in the ALFA trial CSR how many ALFA patients satisfy all these criteria at baseline. It is unclear how many had evidence of tumour lysis and/or disseminated intravascular coagulation, life-threatening bleeding or infection at baseline and so before (and not due to) treatment by 1st line therapies. It is also unclear how many had rapidly increasing white blood cell counts (WBC) at baseline. However, using patient level ALFA data Pfizer calculated that 19.8% of the total Pfizer base-case population and 16.7% of unknown cytogenetic patients had a high WBC (>=30, expressed in 10^9/L). This single criterion suggests 20% is a reasonable estimate of patients that require urgent treatment.

Figure 1. Decision tree representation of stopping rule (scenario 1)



Results

Table 8 presents the cost offsets associated with each scenario and the associated ICERs for the Pfizer base-case population. In the Pfizer base-case population, the cost offsets as a patient average across the population are relatively small and so decrease the ICER by a small amount. This is because the proportion of patients who are affected by the stopping rule is a very small proportion of the total population (0.7% in scenario 1 and 0.9% in scenario 2).

The cost offsets associated with restricted population (favourable and unknowns) are more substantial because ALFA data is used to calculate the relevant proportions and unknowns make up 73.5% of the Restricted population. 18.5% of patients are affected by the stopping rule under scenario 1 (25.9% under scenario 2). The proportion of affected patients is also higher because the proportion of patients not treated based on cytogenetics is higher: intermediate and adverse, compared with just adverse in the Pfizer base-case population scenarios.

It is clear that gemtuzumab ozogamicin is highly cost-effective in the restricted population (favourable + unknown) because the ERG intermediate only ICER was £31,709 and adding the remaining favourable and unknown cytogenetics patients decreased the ERG ICER to £16,910. Applying the cost-offset associated with the stopping rule to the restricted population would make this group even more cost-effective.

Table 8. Results of stopping rule scenario analyses

	Pfizer base-case population		**Restricted population**	
Output	**Scenario 1**	**Scenario 2**	**Scenario 1**	**Scenario 2**
Induction 1 cost offset	£113	£157	£2,955	£4,116
Consolidation 1 total cost offset	£24	£34	£918	£1,279
Consolidation 2 total cost offset	£24	£34	£918	£1,279
New ICER (ERG base-case)	£16,739	£16,672	N/A	N/A
New ICER (Pfizer adjusted)	£15,815	£15,752	N/A	N/A

Conclusion

These scenario analyses, which only account for cost off-sets, suggest a decrease in the ICER for both the Pfizer base case population and population of focus in the ACD. This is simply because the implementation of a stopping rule implies less gemtuzumab ozogamicin use in this arm of the model.

If changes in efficacy could be taken into account, the ICER for the Pfizer base-case population is still unlikely to be affected substantially. This is because of the very small numbers of patients affected as a proportion of the population (< 1%). It is difficult to say in what way the restricted population (favourable + unknown) ICER would be affected if a change in efficacy could also be modelled. If we assume we are withdrawing gemtuzumab ozogamicin treatment from patients in who it is relatively ineffective, it may be safe to assume that relative efficacy and so the ICER would not change significantly.

When assessing the suitability of a stopping rule, considerations about the treatment pathway and practicality of implementing it in clinical practice should also be taken into account. Pfizer has consulted with clinicians and there are doubts about whether such a rule would function as intended in everyday clinical practice; physicians may simply forego the use of GO altogether instead of waiting for the results of cytogenetic testing. Therefore, given that cost-effectiveness in the Pfizer base-case population is not significantly affected by the stopping rule, Pfizer believes that a recommendation for all unknown cytogenetic patients (i.e. without stopping rule) is more appropriate.

Single Technology Appraisal (STA)

Gemtuzumab ozogamicin for treating acute myeloid leukaemia [ID982]

ERG commentary on the response submitted by the company to the ACD

Produced by: CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 Overview

The Evidence Review Group (ERG) was requested by NICE to provide validity checks on the additional scenarios submitted by the company in response to the Appraisal Consultation Document (ACD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and successfully replicated the main results presented by the company.

The company's response to the ACD included:

1 Cost-effectiveness results from an amended version of the ERG's base-case model which includes a revised company base-case.
2 A proposed confidential patient access scheme (PAS) [redacted] The proposed PAS has not yet been approved by PASLU and hence the results including the PAS are not considered further by the ERG;
3 Exploratory analysis – implementation of a "stopping rule", where patients in urgent need of treatment would be treated with GO while results of cytogenetic results are awaited

The company's revised model incorporates several proposed changes to the ERG's base-case analysis including (a) two alternative utility values for the functionally cured heath state; (b) an alternative estimate of the hospitalisation duration for the management of VOD, and (c) an updated survival analysis that incorporates the most recent mortality tables. Further details are provided in Section 2.

2 ERG commentary on the amended company analysis

2.1 Company amendments to the ERG model

The company proposed several further adjustments to the committee's set of preferred assumptions and provided revised ICER estimates for the following populations: (i) patients not known to have unfavourable cytogenetics profile (Pfizer base-case) and (ii) patients with intermediate cytogenetics profile. Although the impact of each of the adjustments was relatively minor, the cumulative impact reduced the deterministic ICER in the intermediate cytogenetics group to under £30,000 per QALY (ranging from £28,813 to £29,682 across 3 separate scenarios).

The amendments made by the company to the committee's preferred assumption are discussed below.

Adjustments to the utility values for the functionally cured patients

The company stated that while they did not disagree with the assumption that functionally cured patients would have lower quality of life than that of the general population, they argued that the ERG's method of adjusting utility values for age resulted in these patients having lower quality of life than patients in the remission health state. The company argued that this was clinically implausible. The ERG notes that the difference in utility values between the functionally cured and remission states arises due to the application of age-adjustments to the functionally cured state from the start of the model time horizon.

The company proposed two alternative values for functionally cured patients: The first was 0.76, which is the TTO derived utility value for functionally cured patients from the TTO utility study undertaken by the company. The second was 0.77, and was taken from the same source as the ERG's but is based on a different mapping algorithm (Proskorovsky et al, 2014). The impact of the application of these utilities in the model was to provide a more consistent pattern of QoL, i.e. that patients' QoL does not suddenly decrease upon entering the functionally cured health state from the remission state.

The ERG considered that the company's approach provides a pragmatic solution to the issue raised by the company. Equally, an alternative approach might be to apply the ERG's age-adjustment from Year 5 onwards (i.e. the time that patients entered the functionally cured state). The company's approach raises the issue of whether it is clinically plausible for there to be differences between the remission and functionally cured states, and the magnitude of any differences. The value from the time trade-off (TTO) study conducted by Pfizer suggested quite important differences between health states. The estimated utility values were 23%-34% higher for the functionally cured state compared to the remission state based on values derived using TTO and VAS approaches, respectively.

Although the ERG notes some caution regarding the different valuation approaches, the magnitude of difference between the utlity values estimates for the functionally cured and remission states does suggest that the utlility values proposed by the company for the functionally cured state (0.76/0.77) appear reasonable compared to the remission state (0.74).

On inspection of the economic model, the ERG noted that the utility selected for the functionally cured health state was also applied to the utility for the remission health state, although the company stated that this utility value would remain as 0.74 (the original value). This resulted in the same implausible situation noted by the company, which was their rationale for implementing this scenario. The ERG subsequently amended the revised company model so that the remission utility was 0.74, which resulted in a minor decrease in the number of incremental QALYs. The results of the ERG corrected analyses are provided in Table 1 alongside the company's original results of these scenarios.

VOD-related inpatient days

The company considered that the excess bed days associated with grade 3-4 VOD (26.8 days), applied by the ERG in their base-case, is an overestimate. Following the ACD, the company consulted with clinicians who suggested a range from 14 to 28 days to be clinically plausible. The company subsequently proposed an alternative estimate based on the mid-point of this range (21 days), which lowered the estimated costs in the GO + DA arm and consequently lowered the ICER.

The ERG notes that the clinically plausible range highlighted by the clinical experts included the estimate that was originally proposed by the ERG. Furthermore, the ERG notes that the duration of excess bed days of 26.8 days is consistent with the period over which the original distutility was applied by the company. The duration of the disutility period was previously reported by the company in their original submission to be a reasonable assumption by clinical experts**.**

Although the ERG recognises that there is some uncertainty regarding the potential magnitude of excess bed days, the ERG does not consider that the company has provided any substantive new evidence to alter this assumption.

Update to mixture cure model parameters

The company re-estimated the base-case MCM curves with background mortality based on more recent lifetables and updated the MCM parameters in the model. These corrections changed the cost-effectiveness estimates marginally. The ERG considers this amendment reasonable.

Patient Access Scheme (PAS)

In their ACD response, the company proposed a PAS consisting of a simple discount of [redacted]. The ERG notes that this PAS has not been approved by PASLU and hence the results are not considered further.

2.2 Results of the company's amendments

The impact of incorporating the company's revised assumptions for the intermediate cytogenetic subgroup is presented in Table 1. This table reports the deterministic estimates reported by the company as well as the corrected deterministic and probabilistic ICER estimates estimated by the ERG.

The cumulative impact of these alternative assumptions reduced the deterministic ICER reported by the company from £31,709 (original ERG base-case) to £28,813-£29,682 per QALY. The equivalent ERG estimates, correcting for the error in the utility for the remission state, resulted in deterministic ICERs between £29,409-£30,091 per QALY. The ERG highlights that the equivalent probabilistic ICERs for this subgroup are higher than the deterministic estimates and range between £32,403 - £34,962 per QALY (ERG corrected estimates).

Table 1 Impact of changes in the model on ICER (intermediate cytogenetics group)

	Deterministic ICER (company)	**Deterministic ICER (ERG-corrected)**	**Probabilistic ICER (95% CI)**	**P(CE) at £20,000**	**P(CE) at £30,000**
ERG base-case	£31,709	£31,709	£34,681 (£30,070 – £40,768)	34%	47%
Company revised base-case (2+3+4)	£28,813	£29,409	£32,403 (£28,108 to £38,066)	33%	47%
Company revised base-case (1+3+4)	£29,682	£30,091	£34,962 (£30,231 to £41,275)	33%	45%
Company revised base-case (2+4)	£28,956	£29,556	£33,355 (£28,957 – £39,149)	33%	47%
Note on company revisions: (1) 0.76 (with aging) utility for functionally cured patients. (2) 0.77 (with aging) utility for functionally cured patients. (3) 21 excess inpatient days for VOD. (4) Updated MCM parameters					

Uncertainty in the intermediate subgroup

In order to quantify the uncertainty in the ICER in the intermediate group, the ERG has estimated the probabilistic ICER for the ERG analysis and the company's scenario analyses. The confidence interval around the probabilistic ICERs includes a lower limit that falls below the £30,000 threshold, but an upper limit that is substantially higher than the £30,000 threshold. In all scenarios, the probability of being cost-effective at a threshold of £30,000 was below 50%.

The subgroup analyses presented by the ERG in their original report were intended to highlight the heterogeneity in prognosis and treatment effect across the different cytogenetic subgroups, and to provide indicative results in each group. The ERG also noted the limitations of these analyses, namely that they were based on smaller patient numbers (the intermediate group was based on 91 patients in the GO arm and 89 patients in the DA arm). Additionally, a further source of uncertainty in these analyses relates to the rates of HSCT. The original ERG analyses made the simplifying assumption that the HSCT rates would be similar to those in the favourable+intermediate+unknown cytogenetic subgroup, as they did not have group-specific data on this outcome.

3 ERG commentary on the "stopping rule" scenario analysis

The committee heard from the clinical experts that if the test results analysis was unsuccessful, it was not routine clinical practice to re-test. The committee agreed that its recommendation regarding patients whose disease had unknown cytogenetics should include those people where the test analysis results was unsuccessful.

The committee requested a cost effectiveness analysis in which patients would receive GO while the cytogenetic results are awaited and treatment with GO would only be continued in course 2 and beyond in patients whose disease had favourable cytogenetics.

The company explored an analysis that specifically examined the unknown group of patients in the ALFA trial (comprising 17 and 12 patients in the GO+DA arm and the DA arm respectively). In the company's scenario analysis, the company estimated the proportion of patients who would avoid unnecessary treatment with GO. These patients were associated with a cost-offset, which resulted in an improvement in the cost-effectiveness estimates.

The calculations in the analysis used the following set of assumptions:

- Patients who were "true unknowns", due to test failure, accounted for 27.6% of the unknown patients in this group. This rate was estimated from the trial publication (Castaigne, 2012), but the ERG was unable to verify this figure.

- It was assumed that the remaining patients with unknown cytogenetics were still waiting for test results.
- Of the remaining unknown cytogenetic patients, it was assumed that the underlying cytogenetic risk was distributed as per the identified patients in the trial.
    - This implicitly suggests that the risk of these patients would ultimately be known, and it would be possible to avoid treating those who would not be eligible for treatment (i.e. unfavourable patients, and intermediate patients based on the committee's initial recommendations).
- 80% were assumed to not require urgent care, and could wait for test results before starting treatment. This figure was based on clinical advice to the company. The proportion of these patients that were unfavourable (and intermediate) were associated with a cost-offset: in the base-case analysis, all of these patients received treatment, but waiting for test results avoids unnecessary treatment.
- Of the 20% of patients who required urgent treatment and received an induction of GO, the proportion who were estimated to be unfavourable (and intermediate) and subsequently achieved a complete response (CR) could avoid further consolidation courses, while in the original model they would incur the cost of these consolidation courses with GO.

The company recognised the need for this analysis to consider adjustments both to cost and lifetime efficacy. However, the small numbers for some of the populations being considered (i.e. unknown due to test results not being available/unsuccessful etc) and the fact that any adjustment would have to be based on strong assumptions since the trial did not directly assess the impact of stopping rules, precluded formal efficacy adjustments. In this scenario, the analysis would require significant changes to the model structure and survival assumptions. The company did not consider they had sufficient evidence to inform these, and hence focused on the potential cost offsets.

The results of these analysis are considered in two populations: the company base-case population (comprising favourable, intermediates and unknowns), and the restricted population (comprising favourable and unknowns). The analysis reduced the ICER in the company base-case population from £16,910 to £16,739, under the ERG's base-case assumptions.

Table 2 Results of stopping rule scenario analyses

Output	Company base-case population[1]		Restricted population[2]	
	Scenario 1	Scenario 2	Scenario 1	Scenario 2
Induction 1 cost offset	£113	£157	£2,955	£4,116
Consolidation 1 total cost offset	£24	£34	£918	£1,279
Consolidation 2 total cost offset	£24	£34	£918	£1,279
New ICER (ERG base-case)	£16,739	£16,672	N/A	N/A

New ICER (company-adjusted)	£15,815	£15,752	N/A	N/A
New ICER (company-adjusted with ERG correction)	£16,054	£15,989	N/A	N/A
[1] Favourable, intermediate and unknown cytogenetics, [2] favourable and unknown cytogenetics. Scenario 1: proportion of unknowns that are not "true unknowns" = 27.6%, Castaigne (2012) (ALFA trial publication) Scenario 2: proportion of unknowns that are not "true unknowns" = 38.4%, Chilton (2017) (pooled sample of AML 12, 14, 15 and 16 trial patients)				

The ERG considered an alternative interpretation of the committee's requested scenario, whereby it is assumed that all of the patients at presentation are unknown, and that a proportion of all patients would receive urgent treatment with GO. Table 3 presents the results for the favourable, intermediate and unknown population, with varying proportions of unfavourable patients who incur the cost of one course of treatment with GO, receive no clinical benefit and considers the disutility and cost of treating adverse events in these patients.

To be consistent with the company analysis and assuming that 20% of patients require urgent care (and thus 20% of unfavourable patients receive induction therapy with GO), the ICER increases from £16,910 to £21,156.

Table 3 ERG analysis (favourable, intermediate and unknown)

Proportion of unfavourable patients receiving one induction course of GO	**ICER**
0%	£16,910
10%	£19,033
20%	£21,156
30%	£23,279
40%	£25,403
50%	£27,526
60%	£29,649
70%	£31,772
80%	£33,895
90%	£36,018
100%	£38,142
Note: ERG analysis based on a framework included by the company in their model: no further adjustments made to these calculations.	

Re: ID982 Appraisal of gemtuzumab ozogamicin

25th July 2018

Dear Professor O'Brien,

Following further discussions with the NICE Technical Team, Pfizer has now submitted a simple Patient Access Scheme (PAS) in our revised set of analyses (providing a [redacted] discount to the list price), which is currently under review by NHSE and PASLU. The results show that gemtuzumab ozogamicin is now cost-effective in the intermediate cytogenetic subgroup when the PAS discount is applied.

Pfizer believes that these revised analyses including the new PAS discount provides the committee with the clarity required to reach a positive recommendation for this clinically important treatment for patients with previously untreated de novo AML when this topic is reconsidered on the 22 August 2018.

With best wishes,

[redacted]

[redacted]

Pfizer revised analyses

During the consultation period, NHSE and Leukaemia Care signalled that the number of urgent cases requiring immediate gemtuzumab ozogamicin treatment was higher than previously discussed and agreed during the first appraisal committee meeting (ACM) held on the 26th of April 2018. The data submitted during the consultation period suggested that approximately 80% of patients are treated within a week of diagnosis of AML. Hence, the committee is now concerned with the wastage costs associated with the treatment of patients for which gemtuzumab ozogamicin provides no clinical benefit and is not considered cost-effective. As a follow-up to the second ACM, the NICE Technical team informed Pfizer that they would like a further analysis undertaken which considers the economic impact of all patients receiving at least one induction cycle of gemtuzumab ozogamicin at presentation.

Based on this request, Pfizer proposed a revised analysis at a teleconference with the NICE Technical Team on the 19th July 2018, which assumed that all patients at presentation are unknown and urgent; hence 100% of patients are treated with one cycle of induction therapy. Patients would continue treatment, with consolidation therapy, only if they have known favourable and intermediate cytogenetics. In this analysis, all the treatment costs of treating non cost-effective patients are included, accounting therefore with the uncertainty related to the "wastage" of treating cost-ineffective patients.

The time lag between induction and consolidation therapies is approximately 3 months. Therefore, it was assumed that, at the time of receiving consolidation therapy the cytogenetics 'profile is known. It was assumed that 21% of patients who would receive consolidation therapy would have unfavourable cytogenetics 'profile, based on the cytogenetics' profile distribution observed in the pivotal trial[1]. As such, the gemtuzumab ozogamicin consolidation treatment costs for this proportion were excluded from the modelling calculations. Gemtuzumab ozogamicin provides no clinical benefit to unfavourable cytogenetic patients and so removing consolidation courses would not be expected to change incremental QALYs.

The results of this revised analysis are presented with 2 model settings: 1. ERG base-case settings, and 2. with accepted (and ERG corrected) Pfizer adjustments taken into account (MCM parameters updated and a 0.77 age adjusted utility value for functionally cured patients). Table 1 and 2 below summarises these results and shows that the resultant probabilistic ICER is less than £21k per QALY

[1] Pfizer. Full Clinical Study Report for Protocol WS936568 (ALFA-0701 [MyloFrance 3]), 15 March 2016.

gained for all de novo AML patients, and for patients with intermediate cytogenetics 'profile the probabilistic ICER remains above £30,000 per QALY gained.

Table 1 – Results, Pfizer proposed analyses (Probabilistic), with ERG base-case settings

Analyses	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
100% Patients treated at presentation[a]	[redacted]	[redacted]	£20,787
Intermediate subgroup only[b]	[redacted]	[redacted]	£33,683

[a] Equivalent deterministic ICER = £19,637 (Incremental costs = [redacted]; Incremental QALYs = [redacted] This is the all patients ICER (i.e. including unfavourable cytogenetics patients) with adjustment. Adjustment made in "RU" tab in cells G51 and G52; default proportions receiving consolidation 1 and 2 in GO+DA arm multiplied by 0.79. Change effects proportion for whom full consolidation course costs apply (cells F46 and F62 in "Cost calcs" sheet).

[b] Equivalent deterministic ICER = £31,709 (Incremental costs = [redacted] Incremental QALYs = [redacted]).

Table 2 – Results, Pfizer proposed analyses (Probabilistic), with accepted Pfizer adjustments

Analyses	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
100% Patients treated at presentation[a]	[redacted]	[redacted]	£19,556
Intermediate subgroup only[b]	[redacted]	[redacted]	£32,991

[a] Equivalent deterministic ICER = £18,809 (Incremental costs = [redacted] Incremental QALYs = [redacted]). This is the all patients ICER (i.e. including unfavourable cytogenetics patients) with adjustment. Adjustment made in "RU" tab in cells G51 and G52; default proportions receiving consolidation 1 and 2 in GO+DA arm multiplied by 0.79. Change effects proportion for whom full consolidation course costs apply (cells F46 and F62 in "Cost calcs" sheet).

[b] Equivalent deterministic ICER = £29,556 (Incremental costs = [redacted]; Incremental QALYs = [redacted]).

Following the meeting with the NICE Technical Team on 19th July 2018, with the focus on intermediate subgroup cost-effectiveness, a simple patient access scheme of [redacted] has now been submitted to NHS England and PASLU for consideration. Table 3 and 4 below show the positive impact on the resultant ICERs when the PAS discount is applied to the acquisition cost of gemtuzumab ozogamicin. The resultant probabilistic ICER for all de novo AML patients is marginally changed and falls below £20K per QALY gained, with the greatest impact observed for patients with intermediate cytogenetics 'profile resulting in a probabilistic ICER which is now less than £30,000 per QALY. Overall, the results show that gemtuzumab ozogamicin is now cost-effective in the intermediate cytogenetic subgroup when the PAS discount is applied.

Pfizer proposed analyses (with confidential [redacted] PAS)

Table 3 – Results, Pfizer proposed analyses (Probabilistic), with ERG base-case settings

Analyses	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
100% Patients treated at presentation[a]	[redacted]	[redacted]	[redacted]
Intermediate subgroup only[b]	[redacted]	[redacted]	[redacted]
[a] Equivalent deterministic ICER = [redacted] (Incremental costs = [redacted]; Incremental QALYs = [redacted]). This is the all patients ICER (i.e. including unfavourable cytogenetics patients) with adjustment. Adjustment made in "RU" tab in cells G51 and G52; default proportions receiving consolidation 1 and 2 in GO+DA arm multiplied by 0.79. Change effects proportion for whom full consolidation course costs apply (cells F46 and F62 in "Cost calcs" sheet). [b] Equivalent deterministic ICER = [redacted] (Incremental costs = [redacted], Incremental QALYs = [redacted]).			

Table 4 – Results, Pfizer proposed analyses (Probabilistic), with accepted Pfizer adjustments

Analyses	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
100% Patients treated at presentation[a]	[redacted]	[redacted]	[redacted]
Intermediate subgroup only[b]	[redacted]	[redacted]	[redacted]
[a] Equivalent deterministic ICER = [redacted] (Incremental costs = [redacted], Incremental QALYs = [redacted]). This is the all patients ICER (i.e. including unfavourable cytogenetics patients) with adjustment. Adjustment made in "RU" tab in cells G51 and G52; default proportions receiving consolidation 1 and 2 in GO+DA arm multiplied by 0.79. Change effects proportion for whom full consolidation course costs apply (cells F46 and F62 in "Cost calcs" sheet). [b] Equivalent deterministic ICER = [redacted] (Incremental costs = [redacted]; Incremental QALYs = [redacted]).			

Single Technology Appraisal (STA)

Gemtuzumab ozogamicin for treating acute myeloid leukaemia [ID982]

ERG commentary on the revised analyses submitted by the company following the 2nd Appraisal Committee Meeting

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **10/08/2018**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 ERG commentary on the revised company analyses

1.1 Company revised analyses

Following the second appraisal committee meeting (ACM) and after further discussion with the NICE technical team, the company submitted additional analyses and a Patient Access Scheme (PAS). The Evidence Review Group (ERG) was requested by NICE to provide additional commentary and validity checks.

The company presented two additional analyses to address the committee's concerns regarding:

(i) the potential impact of including the costs that would be incurred in patients who require urgent treatment while waiting for cytogentic results and who were later found to have unfavourable cytogenetics;
(ii) the cost-effectiveness of treating patients with intermediate cytogentics' profile.

To address the first concern, the company presented a revised analysis which assumed that all patients at presentation have unknown cytogenetics and require urgent treatment. In this analysis, 100% of patients were assumed to be treated with one cycle of induction therapy with gemtuzumab ozogamacin. The analysis further assumed that, at the time a decision is made to proceed (or not) with consolidation therapy, the patients' cytogenetic status would subsequently be known and only patients with known favourable and intermediate cytogenetics would continue treatment with gemtuzumab ozogamacin consolidation therapy. To support the assumption that a patients' cytogentics' profile would be known at the time of receiving consolidation therapy, the company noted that the time lag between induction and consolidation therapies is approximately 3 months

In the revised analysis, it was assumed that 21% of patients would have unfavourable cytogenetics profile, based on the distribution observed in the pivotal trial. The cost of providing gemtuzumab ozogamicin consolidation therapy was adjusted accordingly by excluding the costs of consolidation therapy for this proportion of patients. The clinical effectiveness data for gemtuzumab ozogamacin for this analysis was based on the "all patient" survival analysis. It was assumed that gemtuzumab ozogamacin would not provide any clinical benefit to unfavourable patients and hence removing the consolidation courses would not be expected to change incremental QALYs.

To address the second concern regarding the cost-effectiveness of gemtuzumab ozogamacin in the intermediate cytogenetics subpopulation, the company proposed a simple PAS consisting of a discount of [redacted] The scheme has been submitted to NHS England and PASLU for consideration.

For each scenario, results were presented using two alternative sets of input parameters, based on: (i) the alternative inputs originally proposed by the ERG in their alternative base-case analysis; and (ii) including two additional adjustments proposed by the company in their response to the 1st ACD (an adjustment to the utility values for the functionally cured patients, and an update to mixture cure model [MCM] parameters).

ERG commentary

The ERG was generally satisfied with the interpretation and implementation of the additional analysis. Although the ERG was not provided with the revised company model and analyses, the ERG verified that these were appropriately implemented by amending an earlier version of the model.

One specific issue noted by the ERG concens the company's statement that only patients with known favourable and intermediate cytogenetics would continue treatment with gemtuzumab ozogamacin consolidation therapy. The ERG highlights that this statement appears to exclude consolidation treatment for patients with unknown cytogenetics because the cytogenetic analysis was unsuccessful. However, the ERG notes that the revised analysis presented by the company actually assumes that patients would continue treatment with consolidation therapy only if they were not known to have unfavourable cytogenetics (i.e. including favourable, intermediate or unknown cytogenetics because cytogenetic analysis was unsuccessful). The ERG considers that this broader interpretation is consistent with the committee's provisional recommendations which included people with unknown cytogenetics because cytogentic analysis was unsuccessful and the data and assumptions used by the company.

The ERG previously critiqued the additional adjustments to the ERG's original base-case inputs and concluded that both adjustments proposed by the company appeared reasonable.

1.2 Results of the company's revised analyses

The impact of the company's revised analyses without the confidential PAS applied is presented in Table 1. When all patients were assumed to require urgent treatment and to receive induction therapy with gemtuzumab and only those with favourable, intermediate and unknown cytogenetics continue to receive consolidation treatment, the probabilistic ICER ranged between £[redacted] to £[redacted] per QALY (deterministic ICER range: £[redacted] to £[redacted]. In the intermediate cytogenetics group, the probabilistic ICER ranged between [redacted] and [redacted] per QALY (deterministic ICER range: £[redacted] to £[redacted]).

Table 1 Results of scenario analysis (without proposed PAS)

Scenario	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
Pfizer proposed analyses, with ERG base-case settings – without PAS			
100% Patients treated at presentation	[redacted]	[redacted]	[redacted]
Intermediate subgroup only	[redacted]	[redacted]	[redacted]
Pfizer proposed analyses, with company adjustments – without PAS			
100% Patients treated at presentation	[redacted]	[redacted]	[redacted]
Intermediate subgroup only	[redacted]	[redacted]	[redacted]
Note on company revisions: (1) 0.77 (with aging) utility for functionally cured patients, (2) Updated ixture cure model (MCM) parameters Based on probabilistic analysis			

When the proposed PAS was applied (Table 2), the probabilistic ICER for the intermediate cytogenetics group was reduced to below the £30,000 threshold, and ranged from £[redacted] to [redacted] per QALY (deterministic ICER range: £[redacted] to £[redacted]).

Table 2 Results of scenario analysis (with proposed PAS)

Scenario	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
Pfizer proposed analyses, with ERG base-case settings – with PAS			
100% Patients treated at presentation	[redacted]	[redacted]	[redacted]
Intermediate subgroup only	[redacted]	[redacted]	[redacted]
Pfizer proposed analyses, with company adjustments – with PAS			
100% Patients treated at presentation	[redacted]	[redacted]	[redacted]
Intermediate subgroup only	[redacted]	[redacted]	[redacted]
Note on company revisions: (1) 0.77 (with aging) utility for functionally cured patients, (2) Updated MCM parameters Based on probabilistic analysis			

ERG commentary

The ERG verified the additional analyses and successfully replicated the company's results.