National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Gemtuzumab ozogamacin for untreated de novo acute myeloid leukaemia

Response to consultee and commentator comments re-scope

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 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Population	NCRI-RCP-ACP	Regarding the issue of cytogenetics, all trials have shown that patients with adverse risk disease derive no benefit from the addition of GO but it does not harm them. This raises the issue of getting the cytogenetic data promptly before starting treatment which is not standard practice and may cause difficulty with cytogenetic lab services to produce the results rapidly. However some patients with secondary AML cytogenetics will be known in advance as the patients progress from a previous myelodysplastic syndrome during which cytogenetic analysis had already been made. This will exclude a proportion of patients with adverse cytogenetics from receiving GO who may not benefit.	Comment noted. No action required.
	Pfizer	Pfizer agrees with the addition of the wording “excluding acute promyelocytic leukaemia” to align with exclusion criteria of the ALFA-0701 trial. This subgroup of AML patients is known to have a substantially different prognosis compared to other AML subtypes and the UK clinical pathway is expected to be very different to AML in general.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pfizer	Pfizer does not believe it is necessary to add CD33-positivity as a requirement to the description of the population: - The majority of patients with de novo AML express CD33 as stated in the literature and confirmed by UK clinicians (see also Laszlo GS et al, 2014). o This is supported by the ALFA-0701 trial. CD33 expression on AML blasts was determined in 194/271 (71.6%) of patients overall and few of these patients (13.7%) had low CD33 expression (less than 30% of blasts). - In clinical practice the treatment pathway is independent of CD33-positivity. o The majority of patients with de novo AML will express CD33 which according to UK experts is detected in clinical practice during routine testing in those patients suspected to have AML. o It is standard practice for patients expressing CD33 to receive the same treatments as those who do not, as also seen in UK clinical studies AML 15 and AML 16 which recruited and randomised patients to GO and chemotherapy irrespective of CD33 expression (Burnett et al. 2011; Burnett, 2012). The ongoing UK clinical trials AML 18 and AML 19 do not have entry requirements relating to CD33 expression. - The available evidence base suggests the relative efficacy of GO does not depend on CD33 positivity o The results of the analysis of the effect of CD33 positivity on efficacy outcomes in the ALFA-0701 study demonstrate that the added clinical benefit with the addition of GO to chemotherapy is generally observed for patients with AML independent of the degree of CD33 positivity. Specifically,	Comment noted. Population in scope amended to reflect the positive CHMP opinion.

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		based on subgroup analyses of the effect of GO on EFS in ALFA-0701, it did not appear that degree of CD33 positivity (using 30% and 70% cut-offs) had an impact on the GO treatment effect (see forest plot on pg. 98 of CSR). However, the ALFA-0701 was not designed or powered to prospectively evaluate the benefit of GO compared to the control within or between subgroups of patients defined by CD33 positivity and therefore these trends presented in the CSR should be treated with caution. ○ In addition, the supporting literature (e.g. the IPD meta-analysis. See table 11, pg. 65; figure 10, figure 11, pg. 74) demonstrating that CD33 positivity is not a predictive factor of GO treatment effect. ○ Some literature suggests that patients with low levels of CD33 expression, such as core-binding-factor AML cases, also appear to benefit from treatment with GO suggesting that CD33 expression alone cannot be treated as a predictor of GO efficacy (Appelbaum et al. 2017).	
	Pfizer	It is generally acknowledged that AML is a disease that is highly similar between adults and “teens and young adults” (TYA) therefore in clinical practice these populations can be treated similarly. During the EMA regulatory review Pfizer presented baseline characteristics of the 22 patients younger than 18 that were included in an IPD meta-analysis of patients with AML treated with GO. This comparison suggested that their prognosis is consistent with that of the adult population based on ECOG performance status and cytogenetics (see appendix D.3.1 of the manufacturer submission for full details on the IPD meta-analysis).	

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	Novartis	As per the CHMP opinion, we believe the population wording should be updated to the following “People aged 15 years and older with previously untreated, de novo CD33-positive acute myeloid leukaemia (excluding acute promyelocytic leukaemia)”	Comment noted. Population in scope amended.
Comparators	NCRI-RCP-ACP	The most appropriate comparators for GO in untreated patients has been included in the scope. Standard practice in the UK would be to treat such patients with a combination of Daunorubicin and Cytarabine or the FLAG plus Idarubicin regimen.	Comments noted. The scope has been kept broad. Daunorubicin and cytarabine and the FLAG plus Idarubicin regimen are included in the list of possible comparators. No action required.
	Pfizer	UK clinical expert advice is that standard of care in the UK (outside of clinical trials) for patients with untreated AML is a combination regimen consisting of DA. Therefore this combination should be considered as the main comparator for GO in this appraisal.	Comments noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. No action required.
	Pfizer	Please see the answer to the question above. Pfizer understand, from UK expert opinion, that standard of care in the UK (outside of a clinical trial	Comments noted. The scope has been kept

Section	Consultee/ Commentator	Comments [sic]	Action
		setting) for patients with untreated AML who are eligible for intensive chemotherapy is a combination regimen consisting of DA which is used for induction and consolidation phases of treatment. Therefore this combination should be considered as the main comparator for GO. Please note that there is no maintenance phase in the treatment of AML.	broad. Daunorubicin and cytarabine are included in the list of possible comparators. No action required.
	Pfizer	Clinical experts (including the opinion of a practicing paediatric haematologist) suggested that the clinical pathway for adolescents will be broadly similar to the pathway for adults. The adolescent age group can be treated in adult or paediatric centres. Clinical opinion emphasised that the paediatric clinical pathway is highly similar to that of adults and thus clinical outcomes are comparable. When pathway differences do exist – i.e. treatment with liposomal duanorubicin + cytarabine or mitoxantrone + cytarabine (MA) instead of DA - the impact on outcomes is expected to be similar. When adolescents are not eligible for the high intensity chemotherapy that is established standard of care for adults (DA) it is unlikely they will be eligible for MA either.	Comment noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. No action required.
	NCRI-RCP-ACP	Established clinical practice in the NHS for consolidation of AML would include sequential courses of high dose Cytarabine for patients with good or standard risk disease whereas patients with high risk AML are referred for allo transplant. An important component of definition of high risk is adverse risk cytogenetics but other parameters are important including response to induction therapy, age, WCC at diagnosis and increasingly molecular characteristics based on genomic analysis.	Comment noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. No action required.

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	NCRI-RCP-ACP	Patients aged 15-17 broadly receive the same treatment as older patients, indeed the AML19 trial which recruits widely in this population has just reduced the age of entry to 16 years.	Comment noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. No action required.
Outcomes	NCRI-RCP-ACP	The scope needs to consider the reduction in risk of relapse for patients treated with GO reduces both the need for both salvage chemotherapy at relapse and for transplant in 2nd remission.	Comment noted. 'Reduction in risk of relapse' is captured under the term 'disease-free-survival. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health and Social Care