National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Chronic Lymphocytic Leukaemia (CLL) Support Association	We consider the draft remit and appraisal objective to be appropriate	No action required.
	Lymphoma Association	Yes	No action required.
	GlaxoSmithKline	GSK agrees that this is an appropriate topic for referral.	No action required.
	Napp Pharmaceuticals	Yes we agree this is an appropriate technology for appraisal by NICE	No action required.
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	Yes it is entirely appropriate to refer this topic to NICE for appraisal. Obinutuzumab is not yet licensed but this is anticipated in the next few months. The addition of an anti-CD20 antibody to chlorambucil in patients with CLL who are considered unfit for fludarabine-based therapy is appropriate. This is also being considered for another anti-CD20 antibody, ofatumumab (ID642).	Comment noted. No action required.
Wording	CLL Support Association	We consider the wording of the draft remit reflects the issue.	No action required.

Section	Consultees	Comments	Action
	Lymphoma Association	No comment.	No action required.
	Glaxo Smith Kline	No comment.	No action required.
	Napp Pharmaceuticals	The draft remit/appraisal objective does not indicate if the technology will be appraised as a monotherapy or in combination with other agent/s (e.g. chemo). Once the wording of the proposed licence is known this should be reflected in the draft remit/appraisal objective.	Comment noted. The scope states that the intervention is obinutuzumab in combination with chlorambucil. No action required.
	Napp Pharmaceuticals	The population enrolled in the pivotal phase III trial (CLL 11) assessing the efficacy of obinutuzumab plus chlorambucil were required to have a CIRS score of greater than 6 and/or creatinine clearance < 70 ml/min which would mean they were considered not fit for fludarabine-based therapy. Therefore we feel this should be reflected in the remit/appraisal objective (Goede V, Kirsten Fischer K, Kathryn Humphrey K et al. J Clin Oncol 31, 2013 suppl; abstr 7004; http://clinicaltrials.gov/ct2/show/NCT01010061?term=BO21004&rank=1). A suggested alternative would be "obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia in patients not suitable for fludarabine combination regimens"	The population has been amended to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	The wording of the remit is appropriate.	No action required.

Section	Consultees	Comments	Action
Timing Issues	CLL Support Association	Patients would like to see approval of the appraisal as soon as possible but consideration should be given to the fact that the trial data will not be made public until ASH in December 2013.	Comment noted. The appraisal will be scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
	Lymphoma Association	Depending on how long it takes to achieve marketing authorisation, it may be worth considering an MTA along with ofatumumab in combination with chlorambucil (this was discussed at the scoping meeting for ofatumumab without the panel knowing the draft scope for obinutuzumab was imminent). However, combining the two appraisals risks delay should either be slow getting their licence. There would be additional complexity as the dosing of the chlorambucil was different in the two trials.	Attendees at the scoping workshop agreed that an STA for obinutuzumab was appropriate. This topic has been referred to NICE by the Department of Health as an STA. No action required.
	Glaxo Smith Kline	No comment.	No action required.

Section	Consultees	Comments	Action
	Napp Pharmaceuticals	There are alternative therapies available for the treatment of frontline CLL, including chlorambucil +/- rituximab, bendamustine and fludarabine-containing regimens. Furthermore NICE have reviewed and approved treatments which include - bendamustine (TA216) and rituximab in combination with fludarabine and cyclophosphamide (TA174). Therefore although there is little urgency, we are cognisant that NICE's remit is to review a technology as close to launch as possible	Comment noted. The appraisal will be scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
	Roche Products	In the CLL11 study the addition of obinutuzumab to chlorambucil resulted in an unprecedented leap forward in the outcomes expected for this patient population (PFS HR = 0.14). Due to the magnitude of this efficacy gain an appraisal should be planned as soon as possible.	Comment noted. The appraisal will be scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
	Royal College of Pathologists	Obinutuzumab is likely to obtain marketing authorization in CLL at least in combination with chlorambucil in the near future and then there will be demands for access to the drug for this leukaemia.	Comment noted. The appraisal will be scheduled into the work programme with consideration of the need to provide timely guidance. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft remit		None.	No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	CLL Support Association	No comment.	No action required.
	Lymphoma Association	Line 2: We would suggest adding 'lymphadenopathy' to the problems that CLL causes.	The phrase 'swollen lymph nodes' has been added to the scope.
	GlaxoSmithKline	This is a reasonable reflection of CLL and NICE approved treatment options in the frontline setting.	No action required.
	Napp Pharmaceuticals	No comment.	No action required.
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	The background is accurate and complete. The current on-going consideration of ofatumumab with chlorambucil in CLL is not mentioned but as this is not licensed either or NICE appraised then this is probably appropriate.	Comment noted. No action required.
The technology/ intervention	CLL Support Association	In CLL11 Obinutuzumab was not used with the usual UK Chlorambucil dosage of 70mg/m^2	A sentence has been added to the 'technology' section of the scope regarding the dose of chlorambucil used in the CLL11 trial.
	Lymphoma Association	The trial was specifically in adults with CLL who had not previously received treatment for CLL but did have comorbidities.	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'

Section	Consultees	Comments	Action
	GlaxoSmithKline	Please clarify if obinutuzumab is expected to be used in combination with bendamustine	Attendees at the scoping workshop advised that, in the main phase III trial, obinutuzumab was used in combination with chlorambucil. Attendees advised there was a lack of evidence about the effectiveness of obinutuzumab in combination with bendamustine and a marketing authorisation is not expected for this combination. No action required.
	Napp Pharmaceuticals	Yes.	No action required.
	Roche Products	Obinutuzumab is a type 2 glycoengineered antibody. Obinutuzumab is a new molecular entity and does not currently have a UK marketing authorisation. A marketing authorisation application has been submitted for previously untreated CLL.	Comment noted. The phrase 'type 2 glycoengineered antibody' has been added to the scope.
	Royal College of Pathologists	Yes.	No action required.
Population	CLL Support Association	Obinutuzumab may also be useful for patients already treated and/or are unfit for Fludarabine based regimens. These applications may be subject of future clinical trials.	Comment noted. Guidance will be issued in line with marketing authorisation which is anticipated to be for previously untreated CLL. No action required.

Section	Consultees	Comments	Action
	CLL Support Association	Patients with comorbidities form the population selected for the CLL11 study. The cohort has a median age of 73 these are people with chronic lymphocytic leukaemia who need better treatment options. They form the largest majority of the CLL population and are not able to tolerate FCR due to age and fitness.	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'
	Lymphoma Association	As above, the trial was for adults with CLL and comorbidities. The majority of people diagnosed with CLL are over 60 and likely to have co-morbidities that mean they cannot tolerate the recommended treatment for people who are fitter (FCR). The population is likely to be older people unable to receive FCR and this should be included in the definition of the population.	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'
	GlaxoSmithKline	GSK queries if the target population should be defined as people with previously untreated chronic lymphocytic leukaemia who are considered to be ineligible for fludarabine combination therapy.	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'
	Napp Pharmaceuticals	The population enrolled in the pivotal phase III trial (CLL 11) assessing the efficacy of obinutuzumab plus chlorambucil were considered not suitable for fludarabine containing regimens (CIRS > 6 and relevant comorbidities) so this could be reflected in the remit and scope (Goede V, Kirsten Fischer K, Kathryn Humphrey K et al. J Clin Oncol 31, 2013 suppl; abstr 7004; http://clinicaltrials.gov/ct2/show/NCT01010061?term=BO21004&rank=1).	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	The population is stated as patients with previously untreated chronic lymphocytic leukaemia (CLL). This is appropriate but the technology has only been tested in patients considered unfit for fludarabine-based chemotherapy. These patients should be considered separately.	The population has been changed to 'People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.'

Section	Consultees	Comments	Action
Comparators	CLL Support Association	Fludarabine and cyclophosphamide (with or without rituximab) does not seem an appropriate comparator if the population is people for whom fludarabine combination therapy is not appropriate:	Fludarabine and cyclophosphamide (with or without rituximab) has been removed from the scope.
	Lymphoma Association	Because of the population likely to receive this treatment, it does not seem appropriate for FCR to be a comparator.	Fludarabine and cyclophosphamide (with or without rituximab) has been removed from the scope.
	Lymphoma Association	The other comparators are fine. However, as ofatumumab is currently being considered for use with chlorambucil and bendamustine, chlorambucil plus ofatumumab and bendamustine plus ofatumumab could be considered.	Ofatumumab is not currently in routine use in the NHS. Accordingly, it was agreed at the scoping workshop that ofatumumab is not an appropriate comparator. No action required.
	Lymphoma Association	Alemtuzumab is not a relevant comparator (it is only used first line in patients with p53 deleted CLLIt which is a minority of patients). Reduced FCR is not a suitable comparator as it is still more toxic than the regimens being used in the clinical trials. Most centres would use BR or Chlor-R. Fludarabine single agent is not used widely so should not be a comparator.	Alemtuzumab, reduced-dose FCR (fludarabine and cyclophosphamide and rituximab), and fludarabine monotherapy were not included as comparators in the draft scope. No action required.

Section	Consultees	Comments	Action
	PenTAG	Ofatumumab is due as STA in 2014 for people not suited to Fludarabine. So should ofatumumab be a comparator in this STA, or should the two STAs be combined as one MTA?	Attendees agreed that 2 separate STAs are more appropriate in the interests of timely Guidance. In addition, ofatumumab was not considered an appropriate comparator for this appraisal because it is not currently in routine use in the NHS.
	GlaxoSmithKline	No comment.	No action required.
	Napp Pharmaceuticals	Chlorambucil and bendamustine are suitable comparators as both drugs are routinely used for the frontline treatment of CLL. Recent data would suggest rituximab plus chemotherapy (e.g. chlorambucil) are commonly used combinations in this setting (Hallek et al Am J Hematol. 2013 May 30. doi: 10.1002/ajh.23491. [Epub ahead of print]) and hence rituximab-chlorambucil may be an alternative comparator. Indeed stage 2 of the CLL11 trial will compare rituximab-chlorambucil with obinutuzumab + chlorambucil (data expected Annual Society for Hematology Meeting, Dec 2013). There are also emerging data on the use of rituximab in combination with bendamustine as a firstline treatment for CLL (Fischer et al J Clin Oncol. 2012 Sep 10;30(26):3209-16; Leblond et al 2012 Annual Society Haematology Annual Meeting abstract 2744).	The comparators of chlorambucil (with or without rituximab) and bendamustine (with or without rituximab) were included in the draft scope. No action required.
	Napp Pharmaceuticals	NICE have also recently conducted a draft scoping meeting for ofatumumab + chlorambucil for treatment of frontline CLL so this might also be a reasonable comparator should licensing timelines allow.	Ofatumumab is not currently in routine use in the NHS. Accordingly, it was agreed at the scoping workshop that ofatumumab is not an appropriate comparator. No action required.

Section	Consultees	Comments	Action
	Napp Pharmaceuticals	As the population enrolled in the pivotal phase III trial assessing the efficacy of obinutuzumab plus chlorambucil were considered not suitable for fludarabine containing regimens (Goede V, Kirsten Fischer K, Kathryn Humphrey K et al. J Clin Oncol 31, 2013 suppl; abstr 7004; http://clinicaltrials.gov/ct2/show/NCT01010061?term=BO21004&rank=1), we would not consider fludarabine or fludarabine-containing regimens as appropriate comparators.	Fludarabine and cyclophosphamide (with or without rituximab) has been removed from the scope.
	Roche Products	For patients eligible for fludarabine, FCR is a standard of care. The population recruited into CLL11 is that of a group who are significantly comorbid and/or renal insufficiency and as such would not typically be deemed eligible for intensive regimens such as FC+/-R. In routine clinical practice the majority of these patients are treated with chlorambucil monotherapy and as a result we do not believe fludarabine combination therapies with or without rituximab are appropriate comparators in patients ordinarily treated with chlorambucil.	Fludarabine and cyclophosphamide (with or without rituximab) has been removed from the scope.
	Roche Products	With reference to bendamustine as a potential comparator, we note that the patient population in the RCT evidence supporting the use of bendamustine (Knauf et al. JCO 2009), was a fitter and younger population than seen in routine practice and would commonly receive FCR. Therefore we do not consider bendamustine to be an appropriate comparator to the patient population likely to be considered in a NICE Appraisal based upon the CLL11 study population - who have signifcant comorbities and renal insufficiency and so would be unlikely to be suitable for FCR.	Attendees at the scoping workshop advised that bendamustine (with or without rituximab) is used routinely in the NHS for people who cannot have fludarabine combination chemotherapy. Bendamustine is also recommended by NICE TA216 for people for whom fludarabine combination chemotherapy is unsuitable. For these reasons, bendamustine has been included as a comparator. No action required.

Section	Consultees	Comments	Action
	Royal College of Pathologists	The standard treatments described are appropriate. I think that it is important to include fludarabine-based treatments as a comparator but as these patients were excluded from the German CLL Study Group CLL11 Trial, on which the submission is based, then this cannot be used as a direct comparator.	Fludarabine and cyclophosphamide (with or without rituximab) has been removed from the scope.
Outcomes	CLL Support Association	PFS *[progression-free survival]* is easier to get a clear picture of than OS *[overall survival]*. MRD *[minimal residual disease negativity]* can independently predict for PFS and OS in CLL	Minimal residual disease negativity has been added to the scope.
	CLL Support Association	It should also be noted that Obinutuzumab was used with a low dose of Chlorambucil, not the usual UK dosage.	A sentence has been added to the 'technology' section of the scope regarding the dose of chlorambucil used in the CLL11 trial.
	Lymphoma Association	Overall survival is difficult to capture. The main outcome measure should be progression free survival.	Comment noted. No action required.
	GlaxoSmithKline	No comment.	No action required.
	Napp Pharmaceuticals	Yes.	No action required.
	Roche Products	Minimal residual disease (MRD) should also be considered.	Minimal residual disease negativity has been added to the scope.
	Royal College of Pathologists	Yes however it is not really anticipated that in chronic leukaemias such as CLL that any frontline intervention will impact overall survival. It is widely accepted that progression free survival is the most appropriate primary end-point for such trials.	No action required.
Economic analysis	CLL Support Association	No comment.	No action required.

Section	Consultees	Comments	Action
	Lymphoma Association	No comment.	No action required.
	Glaxo Smith Kline	No comment.	No action required.
	Napp Pharmaceuticals	No comment.	No action required.
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	The proposed economic analysis seems appropriate as does the time horizon.	No action required.
Equality and Diversity	CLL Support Association	As the largest group of CLL patients are diagnosed at an older age with comorbidities and unsuitable for treatment with FCR. Obinutuzumab may positively impact those protected characteristics of age and disability.	Comment noted. No action required.
	Lymphoma Association	No comment.	No action required.
	GlaxoSmithKline	No comment.	No action required.
	Napp Pharmaceuticals	No comment.	No action required.
	Roche Products	No comment.	No action required.
	Royal College of Pathologists	The remit is fine in terms of equality. There are no obvious issues with respect to disability or other equality issues.	No action required.

Section	Consultees	Comments	Action
Innovation	CLL Support Association	This will be the third generation of anti CD20 monoclonal antibodies and as such will be a welcome addition to the treatments available Early results of combination with Chlorambucil in CLL11 are very encouraging and the direct comparison between the Obinutuzumab Chlorambucil combination and Chlorambucil Rituximab will become available in December. There is expected to be a marked improvement in PFS *[progression-free survival]*	Comment noted. No action required.
	Lymphoma Association	The technology is a new generation CD20 antibody and appears to have the potential to offer a new standard of care. The final part of the Phase III CLL11 study comparing obinutuzumab plus chlorambucil with rituximab plus chlorambucil will report at ASH in December 2013. Results already reported at ASCO2013 from the initial stages of this trial show that the obinutuzumab/chlorambucil combination offers a high overall response rate with over a fifth of patients achieving a complete response and acceptable toxicity. The results of the direct comparison with rituximab/chlorambucil are expected to demonstrate improved progression-free survival over its predecessor.	Comment noted. No action required.
	GlaxoSmithKline	No comment.	No action required.
	Napp Pharmaceuticals	Rituximab is an established anti CD-20 antibdy in the treatment of frontline CLL. Obinutuzumab is a fully humanized anti CD20 antibody and a direct comparison between the two has been performed as part of CLL 11 but no data has been published (expected Annual Society for Hematology Meeting, Dec 2013) and hence we are unable to comment on the true innovation of this technology until this data is presented.	Comment noted. No action required.
	Roche Products	Obinutuzumab is a significant step-change in the treatment of CLL. A PFS hazard ratio of 0.14 is unprecedented. A gain of this magnitude represents a leap forward in the treatment of this patient population.	Comment noted. No action required.

Section	Consultees	Comments	Action
	Roche Products	Obinutuzumab is innovative in two distinct ways; being a first-in-class Type II anti-CD20 antibody, and being glycoengineered. Obinutuzumab is expected to be the first Type II CD20 antibody to be licensed for CD20+ve malignancies. In contrast to Type I antibodies, Type II antibodies not only induce CDC and ADCC, but also potently induce direct cell death, and as such induce targeted, anti-leukaemic effects on malignancies such as CLL. Furthermore, through glycoengineering, obinutuzumab potently induces antibody-dependent cellular cytotoxicity (ADCC), being enhanced by up to 100-fold compared with type I antibodies such as rituximab. ADCC is thought to play an important role in anti-leukaemic effect of treatments for CLL. These distinct, innovative characteristics of obinutuzumab are thought to strongly contribute to the results seen in the CLL11 trial. In this trial obinutuzumab demonstrated an ability to eradicate disease to below detectable levels in approximately one third of patients, a proportion surpassing any results previously not seen with current chlorambucil combinations in this patient population. The potency of obinutuzumab combined with a mild chemotherapy such as chlorambucil shows a step-change in outcomes for this little-investigated, yet common patient population.	Comment noted. No action required.

Section	Consultees	Comments	Action
	Roche Products	We note that obinutuzumab may also provide Wider Societal Benefits that are not currently captured in the NICE process. The substantial efficacy gain associated with introduction of obinutuzumab is likely to result in reduced utilisation or "consumption" of both formal and informal care by CLL patients. In addition we note that the outcomes for patients treated with chlorambucil alone are poor (i.e. the Burden of Illness is high) and that, following introduction of Value Based Pricing, this may require explicit consideration by an Appraisal Committee.	Comment noted. No action required.
	Royal College of Pathologists	The addition of an anti-CD20 antibody to chlorambucil is innovative with the potential to have a significant impact for many patients with CLL. Obinutuzumab is a novel anti-CD20 antibody which appears to be active in CLL and may have distinct advantages compared to rituximab meaning that this technology could result in significant and substantial health-related benefits but these should be included in the QALY calculation.	Comment noted. No action required.
Other considerations	CLL Support Association	No comment.	No action required.
	Lymphoma Association	No comment.	No action required.
	GlaxoSmithKline	GSK considers the question to be answered by the appraisal is, if the addition of obinutuzumab to single agent chemotherapy is a cost-effective option for frontline treatment of CLL patients	Comment noted. No action required.
	Napp Pharmaceuticals	Since there are a number of therapies now available for the treatment of frontline CLL approved by NICE, the exact position of this technology in the patient treatment pathway may need to be determined. There is at least one anti-CD20 antibody established in CLL as well as the technology under review. There are also further anti-CD20 antibodies being developed which will be licensed and reviewed imminently (e.g. ofatumumab). The relative therapeutic value of each of these in combination with other agents (e.g. chemo) needs to be understood in the patient treatment pathway.	To avoid a delay in issuing guidance, attendees agreed that an STA for obinutuzumab was appropriate. This topic has been referred to NICE as an STA by the Department of Health.
	Roche Products	No comment.	No action required.

Section	Consultees	Comments	Action
	Royal College of Pathologists	This technology will compete against chlorambucil plus ofatumumab. There are no direct comparative trials between these technologies and there is a separate appraisal being considered for ofatumumab (ID642).	Comment noted. No action required.
Questions for consultation	CLL Support Association	**Which treatments are considered to be established clinical practice in the NHS for previously untreated chronic lymphocytic leukaemia?** With reference to the UK CLL Guidelines, FCR is now the recognised treatment for previously untreated patients who are able to tolerate Fludarabine. Chlorambucil with or without Rituximab and Bendamustine with or without Rituximab are used for those patients not able to tolerate Fludarabine. The new small molecule treatments such as Ibrutinib (Btk inhibitor) are currently being trialled.	The population has been changed to people with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable. Accordingly, FCR has been removed as a comparator.
	CLL Support Association	**Is fludarabine always used in combination with both cyclophosphamide and rituximab in clinical practice?** We believe that Fludarabine should always be combined with Cyclophosphamide and Rituximab (FCR) as stated in the UK CLL Guidelines unless there are good clinical reasons not to.	Comment noted. No action required, because FCR has been removed as a comparator.
	CLL Support Association	**Should fludarabine in combination with cyclophosphamide, and fludarabine in combination with rituximab also be listed as comparators?** FCR is the 'gold standard' treatment and newer treatments should not be compared with FC or FR.	Comment noted. No action required, because FCR has been removed as a comparator.
	CLL Support Association	**Is alemtuzumab still commonly used for treating previously untreated chronic lymphocytic leukaemia and therefore a relevant comparator for this appraisal?** We understand that Alemtuzumab is no longer available. However, it is a useful regimen in certain clinical circumstances but it is not an appropriate comparator for previously untreated patients.	Comment noted. Following discussion at the Scoping Workshop, alemtzumab has not been included as a comparator in the scope.

Section	Consultees	Comments	Action
	CLL Support Association	**Should dose reduced fludarabine, cyclophosphamide and rituximab combination therapy be listed as a comparator, for people who are not able to have fludarabine combination therapy?** We are not able to comment on this question	No action required.
	CLL Support Association	**Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** We are unable to comment fully on the above three questions as the results of the study trial will not be made available until ASH in December 2013. Early data from press releases suggests that the drug will be a useful and beneficial addition to CLL treatments however care should be taken when comparing with other trial data such as Ofatumumab as the Chlorambucil dosage regimens were considerable different.	Comment noted. A sentence has been added to the 'technology' section of the scope regarding the dose of chlorambucil used in the CLL11 trial.
	GlaxoSmithKline	GSK considers the Single Technology Appraisal (STA) Process to be an appropriate one for this assessment.	Comment noted. This topic has been referred to NICE as an STA by the Department of Health.
	Napp Pharmaceuticals	Comments concerning the appropriate comparators and trial population have been highlighted above.	Comment noted. No action required.
	Roche Products	No comment.	No action required.

Section	Consultees	Comments	Action
	Royal College of Pathologists	The most appropriate comparator for the UK is chlorambucil monotherapy for this patient group. The other listed comparators are also important.	Comment noted. No action required.
	Royal College of Pathologists	Fludarabine is always used in combination with both cyclophosphamide and rituximab in clinical practice for CLL. There is no trial data to convincingly support its use with rituximab alone (FR) as is frequently done outside the UK. Therefore fludarabine in combination with rituximab could also be listed as a comparator but there is little data to support its use.	Comment noted. No action required, because FCR has been removed as a comparator.
	Royal College of Pathologists	Alemtuzumab still rarely used for treating previously untreated chronic lymphocytic leukaemia and its use is reserved almost exclusively for a small subset of patients with deletion of chromosome 17p. These patients are not appropriate for chlorambucil-based treatment and is therefore not a relevant comparator for this appraisal. There is little evidence for the use of dose reduced fludarabine, cyclophosphamide and rituximab combination therapy in CLL and it will be difficult for this to be listed as a comparator. There are no specific patient sub-groups in which this technology should be considered except that it will be reserved for those patients who are considered unfit for fludarabine-based therapy.	Comments noted. Alemtuzumab and reduced-dose FCR were not included as comparators in the draft scope. 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, the Royal College of Nursing, Medicines and Healthcare Products Regulatory Agency.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add UK Health Forum	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. UK Health Forum has been added to the matrix of consultees and commentators under 'professional groups'.

2.	Remove British Association for Services to the Elderly	NICE Secretariat		Removed	This organisation ceased to exist in July 2012. Therefore it has been removed from the matrix.
3.	Remove Independent Age	NICE Secretariat		Removed	This organisation no longer wishes to take part in technology appraisals, therefore Independent Age have been removed from the matrix.
4.	Add Alkopharma	NICE Secretariat		Added	Alkopharma has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators.
5.	Remove Actavis UK	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Actavis UK has not been included in the matrix of consultees and commentators.

6.	Remove Baxter healthcare	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Baxter healthcare has not been included in the matrix of consultees and commentators.
7.	Remove GlaxoSmithKline	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; GlaxoSmithKline has not been included in the matrix of consultees and commentators.
8.	Remove Hospira UK	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Hospira UK has not been included in the matrix of consultees and commentators.

9.	Remove Pfizer	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Pfizer has not been included in the matrix of consultees and commentators.
10.	Remove Sandoz	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Sandoz has not been included in the matrix of consultees and commentators.
11.	Remove Sanofi	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Sanofi has not been included in the matrix of consultees and commentators.

12.	Remove Teva UK	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Teva UK has not been included in the matrix of consultees and commentators.
13.	Remove Wockhardt UK	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Wockhardt UK has not been included in the matrix of consultees and commentators.
14.	Remove African Caribbean Leukaemia Trust	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; African Caribbean Leukaemia Trust has not been included in the matrix of consultees and commentators.

15.	Remove Anthony Nolan	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Anthony Nolan has not been included in the matrix of consultees and commentators.
16.	Add HAWC (previously referred to as Help Adolescents with Cancer)	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. HAWC has been added to the matrix of consultees and commentators under 'patient/carer groups'.

17.	Add Aplastic Anaemia Trust	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Aplastic Anaemia Trust has been added to the matrix of consultees and commentators under 'patient/carer groups'.
18.	Remove National Blood Service	NICE Secretariat		Removed	NHS Blood & Transplant was formed from the merger of the National Blood Service and UK Transplant, therefore National Blood Service has been removed from the matrix.