NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia

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

INSTITUTE STATEMENT

Section 6.1.6 of the Guide to the Methods of Technology Appraisal states that; 'The Appraisal Committee is also not normally expected to make recommendations regarding the use of a drug outside its current licensed indications, as published in the manufacturer's Summary of Product Characteristics' (SPC).

Clarification was sought with the MHRA on the issue of the inclusion of the combination of fludarabine and cyclophosphamide in the marketing authorisation of fludarabine. In all correspondence received from the MHRA, including that shared with NICE by Schering Health Care Limited, it has been made clear that 'the MHRA does not consider that the current marketing authorisations for oral and intravenous (i/v) Fludara (PL/0053/0239 & /290) specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia'.

The MHRA has further clarified that, in general, they would expect a manufacturer or sponsor to request a variation in the marketing authorisation when; 1. the SPC in general, and specifically in the 'therapeutic indications' section, does not contain references to the combination therapy and the company wish to promote the use of combination therapy, and 2. the combination use has implications for the specifications in the 'posology and method of administration' section of the SPC. In the case of fludarabine the SPC does not contain references to the combination therapy. With reference to the second point, the dose intensity of the combination of fludarabine with cyclophosphamide (i/v 25 mg/m2 for 3 days and oral 24 mg/m2 for 5 days, in the combination) in the evidence base for the combination therapy that was submitted by the manufacturer (the CLL4 trial) is different from the dose intensity specified in both SPCs (i/v 25 mg/m2 for 5 days and oral 40 mg/m2 for 5 days).

In considering section 6.1.6 of the Guide to the Methods of Technology Appraisal and the in light of the clarification received from the MHRA the Technology Appraisal Programme is not in a position to issue recommendations on the use of fludarabine in combination with cyclophosphamide at this time.

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Schering Health Care Ltd.	I outline in this document our formal response to the appraisal consultation document for the recent appraisal of fludarabine. Our response is organised under the headings specified in your letter. **1. Appraisal consultation document** 1.1 <u>Consideration of relevant evidence</u> • Schering strongly believe that NICE should include the combination of fludarabine and cyclophosphamide within this appraisal. The SmPC for fludarabine does not mention its use in combination with cyclophosphamide however formal clarification from the MHRA has shown that this does not preclude its use in combination. According to the MHRA (see attached- MHRA.doc), "…*Malignancies very often require multiple drugs (and other therapies) and clinicians, expert groups, formulary committees etc are entitled to use/recommend drugs in combination as they see fit*." Consideration should therefore be given to the evidence presented for combination use. • Section 3 of the appraisal consultation document provides a summary of our submission giving key results from the UK CLL4 trial and the cost effectiveness analysis. The incremental cost effectiveness ratio for fludarabine plus cyclophosphamide (FC) compared with chlorambucil, the currently most commonly used first line treatment has been omitted from the summary. The incremental cost effectiveness ratio is £3,244 per quality adjusted life year and this should be included. • No consideration is given to the budget impact associated with a positive recommendation for fludarabine plus cyclophosphamide (FC). Switching patients from current management would increase costs in the first year by around £3.3m, but lower costs of subsequent treatment with FC treated patients in this timeframe mean that the budget impact in year 5 would be negligible, with an annual expenditure in year 5 estimated to be £24.2 vs. £23.5 million with current treatment. 1.2 <u>Interpretation of the clinical and cost effectiveness evidence</u> • The UK CLL4 trial, which compared chlorambucil with fludarabine, either as a monotherapy or in combination with cyclophosphamide is the only study to compare all three treatments relevant to the decision problem within the same population. This is the key trial upon which the submission is	Please refer to the Institute's statement on page one. The Appraisal Committee makes decisions based on clinical and cost effectiveness. As stated in 'The Guide to the Methods of Technology Appraisal' (section 6.2.6.2) the Committee does not consider the affordability of the new technology i.e. the budget impact on the NHS. Comments noted.

Consultee or Commentator	Comment	Institute Response
	based. The trial is sponsored by the Leukaemia Research Fund and patient level data were kindly provided by the Principal Investigators to Schering Health Care for the purposes of this submission. Whilst we recognise this trial is currently unpublished in full it has been presented extensively in abstract form and a full manuscript is in preparation for publication in 2007. Whilst we appreciate the results cannot be verified, the speed of the STA process precludes drafting, peer review and publication of the trial results prior to the NICE submission.	
	• The incremental cost effectiveness ratio for fludarabine plus cyclophosphamide (FC) compared with chlorambucil, the currently most commonly used first line treatment is £3,244 per quality adjusted life year. Results of the probabilistic sensitivity analysis reported by the Evidence Review Group report that at a willingness to pay of £30,000 per QALY the probability that FC is cost effective is 0.90, thus demonstrating clearly the cost effectiveness of this treatment in the management of CLL.	Please refer to the Institute's statement on page one.
	• There is some criticism of the lack of efficacy data for patients receiving retreatment with fludarabine plus cyclophosphamide (FC). The CLL4 trial is ongoing and retreatment data are not yet available. A thorough search of the clinical literature was taken to identify suitable values and in the absence of clinical data extensive sensitivity analyses were conducted.	Comment noted.
	• It appears that some concerns have been raised as to whether the improvement in progression free survival with fludarabine treatment will translate into improved overall survival. The nature of oncology means that after initial treatment patients will ultimately progress and go on to receive subsequent lines of therapy over time, including a range of therapeutic regimens. For this reason it is very difficult to determine the impact of first line treatment on overall survival and therefore progression free survival has become recognised as a suitable proxy for overall survival in this field.	The Committee have been persuaded that progression free survival is an appropriate clinical end-point for CLL patients, as stated in FAD section 4.3.
	• Although the cost of adverse events are not included in the economic model, sensitivity analysis shows that even if the total cost of treatment for fludarabine plus cyclophosphamide (FC) was increased from £3580 to £10,350 per course of therapy the cost effectiveness would remain less than £20,000 per QALY.	Please refer to the Institute's statement on page one.
	• Regarding the expert comments, we believe that Professor Hamblin's perception of the side-effects of fludarabine doesn't fully reflect the scientific evidence from both our pharmacovigilance database and from what has been reported in the literature. In particular we do not believe that there is an increased risk of second malignancy with fludarabine and there is no increase of Richter's transformation associated with fludarabine. In addition, we have also reviewed the incidence of MDS/AML in patients who have received fludarabine, and we do not believe at this stage that there	Comment noted.

Consultee or Commentator	Comment	Institute Response
	is an increased risk with fludarabine, above other treatments for CLL. However, our pharmacovigilance department are monitoring this closely. We are aware of a number of publications reporting on series of patients who have developed MDS/AML, but we believe that the methodology of most these studies are seriously flawed. 1.3 Provisional recommendations of the appraisal committee • The provisional recommendations of the appraisal committee fail to consider the use of fludarabine and cyclophosphamide (FC) in combination. Clinical data clearly demonstrate that the reduced dose of fludarabine when used as part of this combination regimen demonstrates significant improvements in response rate and response duration, at a reduced cost to fludarabine monotherapy. The FC treatment option therefore dominates fludarabine monotherapy and has a cost per QALY of £3,244 when compared with chlorambucil. This cost effectiveness ratio is relatively insensitive to variation in inputs and assumptions. **2. Evaluation Report** 2.1 Interpretation of the clinical and cost effectiveness evidence • The results of the seminal study by Rai and colleagues [NEJM, 2000, 343: 1750-1757] have not been reported accurately. Within the results section (page 26 of the evidence review group report) progression free survival is stated as being 20 months for F versus 14 months for FC, but the latter treatment should have been reported as Chlorambucil (PFS difference between F and Chlorambucil, $p < 0.001$). The same typo error is also repeated on page 19 within the table of the summary of trials. The correct data is listed on page 39. We would like to point out that in chapter 2 of the evidence review group report, section 2.1.4, that the description of treatment is incorrect. The reference 17 [ESMO guidelines, 2005] does not state that "patients with advanced or progressive disease should be initiated with fludarabine in combination with either chlorambucil or chlorambucil with rituximab", but recommends that the patients should receive fludarabine in combination with cyclophosphamide.	Please refer to the Institute's statement on page one. Comment noted. Comment noted.
Nominated patient experts and clinical specialists		
Clinical Specialist	It has been apparent for 10 years that fludarabine is an effective drug in CLL. At that time the standard treatment for CLL was an alkylating agent, usually chlorambucil but in patients who were intolerant to this	Comment noted.

Consultee or Commentator	Comment	Institute Response
Professor Terry Hamblin Nominated by Leukaemia Research Fund.	drug cyclophosphamide was substituted. When oncologists find two drugs that are effective in the treatment of a malignant disease, then their natural instinct is to combine them. The CALGB trial published in the New England Journal in 2000 (Rai et al) included the fludarabine + chlorambucil combination, but this was considered too toxic. Subsequently the combination of fludarabine + cyclophosphamide has been demonstrated in 3 randomised clinical trials to be superior to fludarabine alone in the following respects: it produces more overall responses and more complete responses, it produces longer remissions, and it is cheaper. Moreover, the toxicity of the combination is tolerable and does not add significant extra costs. In one randomised clinical trial (LRF CLL4) it is also superior to chlorambucil in overall remissions, complete remissions, and length of remission. It is of course more expensive than chlorambucil. Because CLL is a chronic disease and because during the course of the disease the patient may have three, four, five or even six rounds of treatment which may be of the same or different drugs, it will never be possible demonstrate an overall survival advantage for a particular type of treatment given as first line, unless that treatment cures the disease. Nor is it likely that trials will be able to demonstrate that a particular sequence of treatment is preferable. We must work within the limitations of what data are available. I am aware that the FC combination has not been commented on because there is no marketing authorisation fro the combination. This seems to me to be a mistake, especially so, as we know the evaluation has been done and the decision is likely to be favourable. The fact is that virtually all cytotoxic drugs are given in combinations, and it would be perfectly reasonable for NICE to recommend that fludarabine should ordinarily be given in combination with cyclophosphamide. For many years the standard therapy for acute myeloid leukaemia employed Daunorubicin in combination, an unlicensed indication. It seems to me that the reputation of NICE depends on it making recommendations that relate to real life rather than to some paper world that exists only in the minds of those who don't treat patients. I think I am well known as someone who believes that the rest of the world has discarded chlorambucil in the treatment of CLL far too easily. Nevertheless, to recommend that the FC combination not be used as first line treatment for some cases of CLL in NHS hospitals is such a distortion of the evidence as to make those making the recommendation a laughing stock in the eyes of patients and doctors alike. I realise that NICE is not saying that, but to fail to make a recommendation in favour of the combination comes to the same thing. People will undoubtedly say that NICE is hiding behind a technicality. I fully understand why NICE is not making a recommendation on the combination, but it will reflect very badly on the reputation of NICE if it does not do so. Some method of surmounting this difficulty must be found.	Comment noted. Comment noted. Comment noted. Please refer to the Institute's statement on page one. Comment noted.

Consultee or Commentator	Comment	Institute Response
Clinical Expert Dr Andrew Pettitt Consultant Haematologist Nominated by British Committee for Standards in Haematology	Thank you for inviting me to comment on the provisional guidance on the use of fludarabine in the first-line treatment of CLL. I am sorry to say that I think NICE have made a grave tactical error in restricting the appraisal to fludarabine monotherapy. By choosing to make an issue out of a licensing technicality, NICE is effectively denying CLL patients in the UK access to a therapeutic regimen that the whole world considers to be the new gold standard. This would be bad for patients, bad for future clinical trials, and bad for UK credibility in the international arena. I could understand NICE's position more easily if there was a major cost implication, but there isn't! The current license for fludarabine does not specify that the drug should not be used in combination with other chemotherapeutic agents, and the latter idea is adequately covered in the cyclophosphamide license. Based on these considerations, my strong and clear advice as one of the nominated expert advisors involved in the appraisal is that NICE should retract its provisional recommendations and issue new guidance that takes into account the overwhelming body of data supporting the use fludarabine in combination with cyclophosphamide in the first-line setting.	Please refer to the Institute's statement on page one. Please note that this does not imply a negative recommendation for the combination of fludarabine and cyclophosphamide.
Patient Expert Jane Barnard Nominated by Chronic Lymphocytic Leukaemia Support Association	<u>Reply to the Recommendation of NICE on Fludarabine STA.</u> I believe that your recommendation that Fludarabine should *not* be recommended for first line treatment of CLL (chronic Lymphocytic leukaemia) is in error. I further believe that your contention that 'no recommendations can be made in respect to fludarabine plus cycloposphamide' combination is also in error. My reasoning is, briefly, as follows: The contention of NICE is that overall the data used to generate the study is incomplete. In the sense that the drug manufacturer has seen fit to delete some data I concur that this is, at best, unfortunate. On a broader scale, it is inevitable that directly comparing studies will be problematic since population selection and dosages of the drugs will necessarily vary. Additionally, NICE contends with justification that the CLL 4 study is 'not complete'. Treatment studies with drugs for CLL are essentially carried out with (thankfully) small populations since numbers of CLL patients are, compared to the general population, rare. Fewer are chemotherapy naive patients, as the disease has a long development time. Hence, whatever the theoretical end point of the study, given a disease with a 'mean' survival time of (opinions vary) 16 years, it is not feasible to 'complete' the study and the UK should take advantage of new developments. *These disease features should not be used to deny the use of fludarabine in first line cll treatment when the empirical data strongly suggests a hugely more effective result than chlorambucil, especially in combination with cycloposphamide.* The combination of fludarabine with cycloposphamide has advantages over fludarabine alone. Prof.	Please refer to the Institute's statement on page one. Comment noted. Comment noted. Comment noted. Comment noted. All relevant costs are considered in the appraisal.

Consultee or Commentator	Comment	Institute Response
	Hamblin said words to the effect that, cycloposphamide, as an immunosuppressant, appeared to give a protective effect from AIHA instigated by fludarabine treatment in some patients. *The addition of cycloposphamide to fludarabine treatment adds pence to the total, and benefits to those patients that have to undergo treatment. I suggest that it is ethical of the manufacturer to assume/request licensing in this case.* NICE states that re-treatment rates and cost of treating patients who have suffered adverse effects from fludarabine have not been calculated correctly, or not included. The physicians treating the patients must consider that the possible effects of treatment are still, on balance, in the patients' favour or they would not treat. There are also costs to be assumed if patients are not treated at all; hospitalisation for varying lengths of time is feasible in all cases. The clinical experts have stated that effectively triage will take place to select patients who would *benefit* from fludarabine monotherapy or in combination. To some extent the costs of re treatment or treatment for adverse effects cannot be calculated. I would add here that the contention of the clinical experts that all cll patients should be tested for the relevant markers has justification, since they directly affect the most effective type of treatment in some patients NICE contends that progression free survival does not equate with overall survival. I cannot argue that this is untrue; however, I contend that barring evidence to the contrary, that 'progression free survival' equates with overall survival is a very reasonable assumption. Humans are long lived, and there is no comparable animal model. The disease has long progression. I submit that waiting for more data could be construed as prevaricating. *To conclude, I believe that NICE has sufficient evidence to approve fludarabine, and fludarabine in combination with cycloposphamide, as a front line treatment for CLL where the physician believes that it is appropriate.*	Comment noted. Comment noted. Comment noted.
Patient Expert Dr Howard Pearce Chairman of the Chronic Lymphocytic Leukaemia Support Association	I give below my comments on the ACD on Fludarabine :- (i) *Whether you consider that all of the relevant evidence has been taken into account* We do not consider that the evidence relating to the use of Fludarabine in combination with Cyclophosphamide has been fairly considered. Restricting the Appraisal Committee's guidance to Fludarabine alone is blinkered and short sighted. It ignores the submissions of both Clinical Experts and both Patient Experts to NICE who support the use of Fludarabine in combination therapy with Cyclophosphamide as it produces a higher response rate and longer remissions.It also ignores the fact that on a worldwide basis Fludarabine in combination with	Please refer to the Institute's statement on page one. Comment noted. Comment noted.

Consultee or Commentator	Comment	Institute Response
	Cyclophosphamide ,and often also with Rituximab, is increasingly seen as the gold standard for treatment of CLL. In other words other countries have analyzed the same data available to NICE on Fludarabine and reached a diametrically opposed conclusion !!	
	(ii) *Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate*	Comment noted.
	Again these summaries are flawed as they focus on Fludarabine monotherapy.However given the opportunity that this review provides we strongly recommend that all available evidence is collected to enable full consideration now of ICER's for a comparison of Fludarabine/Cyclophosphamide treatment versus Chlorambucil. Failure to do this now would represent a major lost opportunity and deny many UK CLL patients a treatment which demonstrably gives better responses and longer remissions.	Comment noted.
	(iii) *Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS*.	
	As is clear from our comments above we do not consider that the ACD recommendations are sound and if confirmed would represent a major lost opportunity for CLL patients in the UK. There would continue to be a postcode lottery in the provision of Fludarabine in the UK and many patients would be denied a better treatment.	Comment noted.
	We agree with the AC recommendation that prognostic marker tests should be used to better identify sub groups of patients who would benefit from Fludarabine. There has already been extensive research on this and several tests are now widely available but are not generally offered on the NHS. We would like to see ALL CLL patients benefiting from these prognostic tests as a matter of routine and Fludarabine being approved as a treatment option for suitable patients.	Comment noted.
Professional and Patient Groups		
British Committee for Standards in Haematology	Response to Appraisal Consultation Document of the STA of fludarabine for the treatment of lymphocytic leukaemia	
	1. The STA has reviewed all the relevant trial information on the use of fludarabine alone and in combination for the first line treatment of B-CLL though it has excluded useful data from its conclusions on debatable grounds (e.g. the studies reported by Johnson and Leporrier on the grounds that CHOP or CAP are not routinely used in CLL patients in the UK). It is not clear how the application of such selection criteria affect the validity of the data derived from those patients	Comments noted.

Consultee or Commentator	Comment	Institute Response
	treated with fludarabine; these studies emphasise the long duration of fludarabine use in clinical practice and contribute useful data on response rates at the time of re-treatment. Eighty five per cent of patients previously responsive to fludarabine respond to re-treatment with the same agent but the response rate falls to 12% in patients who are refractory to previous fludarabine therapy. A Cochrane review of single-agent purine analogues has been published since the completion of the ERG's report (Steurer et al Cancer Treat Rev 2006; 32:377-89) which concluded that 'there was a trend for improved overall survival for patients receiving purine analogues as initial therapy but statistical significance was just not reached (HR 0.89[95% CI 0.78-1.01])'. This is an encouraging finding in the context of the efficacy of purine analogue salvage therapy in patients receiving alkylator based treatment initially and its effect on improving the survival results of this group. The report also noted that 'the RR for achieving an overall (RR 1.22[95% CI 1.13-1.31]) and complete response (RR 1.94 [95% CI 1.65-2.28]) was significantly improved resulting in a longer progression free survival (HR 0.70 [95% CI 0.61-0.82])'.	
	2. The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence but should explicitly acknowledge the high likelihood of fludarabine use at re-treatment in the total cost of treating a patient (i.e. chlorambucil may be cheap and moderately effective first line therapy but you are still likely to need fludarabine based treatment later).	Comment noted
	3. The provisional recommendations of the Appraisal Committee are clinically inappropriate and will be detrimental to patients because of the arbitrary decision not to consider the use of fludarabine plus cyclophosphamide (FC). The BCSH guidelines for the management of CLL are currently under revision and the authors' analysis of the new trial data available since the last version concludes that 'current strategies for the management of CLL, particularly in those patients with good performance status, mirror those in other haematological malignancies and seek to achieve Minimal Residual Disease (MRD) negative responses. An important consideration on beginning treatment in CLL is whether to adopt a palliative approach and treat symptomatic disease with regimens causing minimal treatment-related toxicity, or to aim for prolonged disease-free survival in the hope that this will translate into superior overall survival. Two recent studies have shown that patients who achieve MRD negativity have a survival advantage and this should therefore be the therapeutic aim in all patients fit enough to receive chemotherapy regimens capable of achieving MRD negativity (Bosch 2003, Moreton 2005)'. MRD negativity can only be realistically obtained by the use of fludarabine combination therapy such as FC so the guidelines propose that 'for the majority of patients who are ineligible for a transplant procedure and in whom there is no contraindication to fludarabine e.g. renal failure, the first line treatment should be combination chemotherapy with fludarabine and cyclophosphaminde (grade A recommendation, level 1b evidence). Both fludarabine and chlorambucil are options for patients who are deemed unfit for combination FC therapy (grade A recommendation, level 1a evidence)'.	Please refer to the Institute's statement on page one. Please note that this does not imply a negative recommendation for the combination of fludarabine and cyclophosphamide.

Consultee or Commentator	Comment	Institute Response
	By fixing the review date of this STA at 2009, NIHCE will effectively deny patients with CLL access to effective and cost-effective treatment as most Clinical Haematology Departments in the UK will be refused funding for FC by their PCTs for treatment that has not been endorsed. In this context the ACD's call for further research is unhelpful and inappropriate since it appears to be simply a tactic for avoiding the task of addressing the clinically appropriate question of whether fludarabine plus cyclophosphamide is an effective and cost-effective treatment of CLL. Indeed the data in the STA clearly shows this to be the case on the evidence currently available. Research into prognostic markers as a means of selecting treatment for patients with CLL is well advanced and is incorporated into the planning of the next generation of trials within the UK. Unfortunately the next principal initial therapy study (CLL6 comparing FC plus Mitozantrone with FCM plus Rituximab) has not received funding support from the MRC so the research questions will remain unanswered in the UK and British patients will have no opportunity to enter a trial with the chance of achieving MRD negativity. It will present haematologists with an interesting problem in obtaining consent from patients with CLL who require therapy when they are obliged to explain that the only funded choice of treatment available to them is chlorambucil while recent trials data and the national guidelines suggests that they would be most effectively treated with fludarabine plus cyclophosphamide	Please refer to the Institute's statement on page one. Please refer to the Institute's statement on page one.
CancerBACUP	**Fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia** **Cancerbackup welcomes the opportunity to contribute to the appraisal of fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia (CLL). As the leading specialist provider of independent information on all types of cancer, Cancerbackup has regular contact with people living with CLL and those caring for them.** Last year Cancerbackup received over 1,036 telephone enquiries about leukaemia over 26,000 visitors to our website pages on CLL. Cancerbackup believes that everyone with cancer should be offered the most effective and appropriate treatment, based on the available evidence and the patient's own wishes and preferences. We believe that: • Patients should have access to the most effective treatments appropriate to them as individuals; • Patients should be able to choose – in partnership with their oncologist – the treatment that is likely to suit them best in terms of relative benefits and side-effects;	Comments noted. Comment noted. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of

Consultee or Commentator	Comment	Institute Response
	• The impact of treatments on patient's quality of life, as well as length of life, should be given full consideration by the Appraisal Committee. Cancerbackup is disappointed that the ACD does not recommend the use of fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia and urges NICE to reconsider and approve this technology. **Living with Chronic Lymphocytic Leukaemia (CLL)** At the moment, CLL is not regarded as curable. However, treatments are very successful in getting most people into remission, which can last for a number of years. The aim of treatments is to allow patients with CLL to have a normal life for as long as possible with no symptoms. **Fludarabine Monotherapy** As the ACD notes early results from the CLL4 trial show clear benefits for patients in the use of fludarabine monotherapy compared to chlorambucil with response rates of 77% for fludarabine monotherapy and 69% for chlorambucil; and 3 year progression free survival of 31% for fludarabine monotherapy and 23% for chlorambucil. Patients receiving fludarabine may experience side effects including; a lowered resistance to infection, bruising or bleeding, anaemia, loss of appetite, fever, chills and joint pain and tiredness and a general feeling of weakness. **Scope of Appraisal** Whilst we understand NICE can only appraise treatments for their licensed indications we are disappointed that NICE do not appear to acknowledge the affect that rejecting fludarabine as a monotherapy will have on patients whose clinicians have recommend fludarabine in combination with cyclophosphamide (FC). The CLL4 study clearly shows higher response rates (90%) and higher 3 year progression free survival rates (62%) than fludarabine monotherapy. FC is widely used as a treatment for patients with CLL and we are seriously concerned that negative NICE guidance on fludarabine as a monotherapy will prevent the use of FC. **Final Appraisal Determination** Cancerbackup argues that NICE should recommend that fludarabine monotherapy is available on the NHS for the first line treatment of patients with chronic lymphocytic leukaemia. Fludarabine is an important treatment for patients with CLL and must be available as a treatment option	economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5) Comment noted. Comment noted. Comment noted. As stated in section 4.11 of the final appraisal determination, the Committee is unable to recommend fludarabine monotherapy for first line

Consultee or Commentator	Comment	Institute Response
	where patients and clinicians agree it is the best option. Cancerbackup believes that people with cancer should have the right to make an informed choice about their own care and treatment. NICE's final guidance should reflect the right of patients to make decisions, in consultation with their clinicians, about their treatment. Crucially, if the Appraisal Committee decides to uphold the negative guidance given in the ACD, NICE must ensure that: **1. Patients currently being given fludarabine should have the option to continue their treatment** The Appraisal Consultation Document fails to note that this technology is already being prescribed. If fludarabine monotherapy is not recommended for use then the Final Appraisal Determination (FAD) must specify that those patients currently being given fludarabine for first line treatment of chronic lymphocytic leukaemia should have the option to continue their treatment. Otherwise, there is a risk that these patients will have treatment withdrawn. **2. The FAD clearly relates only to the use of fludarabine as a monotherapy** As described above we are seriously concerned that negative NICE guidance on fludarabine as a monotherapy will prevent the use of FC. The FAD must not prohibit the use of fludarabine in combination use, and must clearly state that this is the case. **3. NICE should recommend the use of fludarabine in further clinical trials** Further trials are needed to further determine the effectiveness of fludarabine in treating chronic lymphocytic leukaemia. **Declaration of interest** Cancerbackup has received sponsorship for several publications and projects from Schering Health Care Ltd, the manufacturer of fludarabine.	treatment of CLL as a cost effective use of NHS resources. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5) NICE technology appraisal guidance is prospective, therefore patients who are currently receiving fludarabine for CLL should have the option to continue therapy until they and their clinicians consider it appropriate to stop. Please note that this does not imply a negative recommendation for the combination of fludarabine and cyclophosphamide. Comment noted. Comment noted.

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CHILDREN with LUEKAEMIA	Thank you very much for inviting CHILDREN with LUEKAEMIA to comment on this STA. I have consulted extensively with our medical colleagues at Great Ormond Street hospital who treat childhood leukaemia. Although they occasionally use Fludarabine for acute childhood leukaemia, they confirmed that children do not develop chronic lymphocytic leukaemia and therefore I do not feel it is appropriate or helpful for us to comment on this STA. We would, however, be very interested in taking part in any future NICE consultation processes, particularly those relating to leukaemia in children.	Comments noted.
Royal College of Pathologists	**Fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia** The College is disappointed by the recommendations in NICE's Final Appraisal Determination. We feel the failure of NICE to widen their scope to include the data on fludarabine and cyclophosphamide has led to a narrow determination which may remove the funding of a proven front – line therapy in CLL and singularly fails to take into account the full role of fludarabine in the treatment of CLL. It is an excellent example of narrowing the scope leading to a determination that may deny patients a front – line therapy that has not been assessed. The Appraisal Consultation Document also fails to note that this technology is already being prescribed. The recommendations in NICE's Final Appraisal Determination should specify that those patients currently being given fludarabine for first line treatment of chronic lymphocytic leukaemia should have the option to continue their treatment. Otherwise, there is a risk that these patients will receive a substandard, less suitable treatment. NICE's final guidance should also reflect the right of patients to make decisions, in consultation with their clinicians, about their own treatments. NICE must also consider recommending the use of fludarabine in further clinical trials.	Please refer to the Institute's statement on page one. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5).

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Medicines and Healthcare Products Regulatory Agency (MHRA)		
	Although, we do not consider that the current marketing authorisations for oral and IV Fludara (PLs 00053/0239 & /0290) provide a recommendation that fludarabine and cyclophosphamide can be used concurrently for the treatment of chronic lymphocytic leukaemia, it does no preclude concurrent use. Malignancies very often require multiple drugs (and other therapies) and clinicians, expert groups, formulary committees etc are entitled to use/recommend drugs in combination as they see fit. An analogous situation is an SmPC for an antihypertensive would not necessarily contain all possible BP lowering regimens.	Comments noted.
Department of Health		
	Thank you for inviting the Department of Health to comment on NICE's Appraisal Consultation Document on Fludarabine, for the treatment of lymphocytic leukaemia. The Department has no substantive comments to make, though colleagues noted that the key trial in the Fludarabine appraisal has limited follow-up, with no known survival difference, and very limited quality of life data. This is presumably reflected in the wide range of cost effectiveness estimates.	Comments noted.
Commentators		
National Cancer Research Haematology Clinical Studies Group	On behalf of the National Cancer Research Haematology Clinical Studies Group I must express serious anxieties about the decision of NICE not to support the use of fludarabine combined with cyclophosphamide (FC) in the first line treatment of patients with chronic lymphocytic leukaemia (CLL). This decision has important implications for the conduct of research in this area in the UK and threatens our research position vis à vis the rest of the world. The FC combination has been proven to be more effective in terms of response rates and progression-free survival when compared fludarabine or chlorambucil in three large international clinical trials. The largest of these was the UK's LRF CLL4 trial in which the complete response rate was increased from 15% for fludarabine monotherapy to 39% for FC. I do not think that these findings are likely to change significantly with further follow-up. In addition, in a chronic condition such as CLL, with the opportunity for treatment crossover after relapse, it will be near impossible to detect improvements of new treatments in overall survival. The competitive ICER per QALY for the combination of FC compared with single agent fludarabine suggests that this is both an effective and affordable combination. The LRF CLL4 trial demonstrates the lowest rates of haemolytic anaemia for this combination and the trial does not demonstrate one of your expert's assertions that haemolysis is more severe in patients receiving fludarabine. In my view the ERGs comments on the additional costs of antimicrobial prophylaxis for	Please refer to the Institute's statement on page one.

Consultee or Commentator	Comment	Institute Response
	patients receiving fludarabine are unlikely to be relevant. The costs for pneumocystis prophylaxis is small and it is by no means clear that patients should receive prophylaxis for herpes and this is not universal practice.	
	The LRF CLL4 trial was the largest CLL trial ever performed from within the NCRI portfolio and has been one of the most successful. The size of the advantage was more than could reasonably have been expected beforehand. The trial was carried out largely in the United Kingdom. The failure to adopt the results of such a successful trial for all suitable patients in the UK sends a clear message that the NCRI trials mechanism is failing. What is the point of performing these well-designed and successful trials if the National Health Service is going to completely ignore the results and not adopt the most effective therapies?	The CLL4 trial provides the largest part of the evidence provided for this appraisal. However, the Committee has interpreted the data provided from the CLL4 trial with caution because the follow-up period for the CLL4 trial was not complete (see FAD section 3.4).
	Not only is FC more effective than fludarabine monotherapy but the acquisition costs of the drugs are significantly less. In addition, the markedly prolonged progression-free survival for FC means that patients do not require salvage therapy early in their disease. If patients are treated in accordance with this draft guidance as well as the NICE Guidance No. 29 from September 2001 then they would receive chlorambucil initially followed by fludarabine monotherapy at relapse. At second relapse they would most likely receive FC and at further relapses alternative salvage therapies. Alternatively if patients received FC as their initial therapy this would reduce the overall cost of their treatment. Therefore not only are NICE recommending the least effective drug in CLL (chlorambucil) but also a treatment strategy that may be more expensive in the longer term. This makes no clinical or economic sense.	Please refer to the Institute's statement on page one.
	I agree that fludarabine (or FC) is not suitable for all patients and that for some chlorambucil produces a good treatment response and worthwhile benefits. However it should not be forgotten that there remains a large number of younger patients and those without co-morbidity with poor prognosis disease who are able to tolerate FC and who will benefit from the improved progression free survival.	Please refer to the Institute's statement on page one.
	It is clear that the Committee have had some difficulty with the combination FC – some analysis has been performed on the benefits but then it has been dismissed because of a technicality with regards to licensing. I am not sure how this can be overcome however I remain of the view that an inability to use FC as a backbone to new trials in CLL in the UK will significantly undermine our position to remain a competitive and credible force in this area. I understand that the SMC will include a statement concerning the utility of the FC and I wonder if NICE would be able to find a way to accept the FC combination within a trial setting.	Please refer to the Institute's statement on page one.

Reply received but no comments:

- none

Comments received from website consultation:

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
NHS Professional 1		As a practicing clinician and member of the UK CLL clinical Trials Forum, I would personally like to comment on the NICE proposal not to recommend fludarabine as first line therapy for patients who require treatment. I see it my duty as a patient advocate to explain my personal views:	Please refer to the Institute's statement on page one.
		1) The CLL 4 study clearly shows that fludarabine has little to no advantage over chlorambucil but that is not true of fludarabine / cyclophospahamide (FC)combination therapy. It is clear therefore that FC requires approving and not fludarabine alone.	Please refer to the Institute's statement on page one.
		2) CLL is not like any other cancer. Studies have shown that those patients who die of CLL have on average 6 different therapeutic regimens from diagnosis to death i.e. they have virtually all the treatments available. Historically one has used the smallest "hammer" i.e. chlorambucil, before moving onto "bigger" hammers such as fludarabine alone or in combination or antibody therapy - rituximab, alemtuzumab, transplantation etc. Thus historically one starts with the cheapest therapies which means one ends up giving the most intensive and expensive therapies to patients who have already received many different therapies, have developed co-morbidities due either to age or disease progression and who are many years older and hence less likely to live long enough to get the full benefits of these more intensive therapies. Average survival for CLL patients requiring treatment is 8 years so no studies have been or ever will be able to show an Overall Survival difference as they are simply either not powered to do so or it is too complex to define how much each of the 6 therapies contributed to survival. If you think it through you will actually save money by using FC upfront as opposed to later in the course of disease.	Please refer to the Institute's statement on page one.
		3) The German Fludarabine versus FC randomised study is about to publish it's toxicity data. There was no pneumocystis, bacterial or viral prophylaxis given at all and despite this the infections rates are similar and very low - indeed the new National guidelines for CLL management will not recommend any antimicrobial prophylaxis at all for newly diagnosed patients commencing purine analogue therapy. Clearly by using the smaller to larger hammer treatment pathway (as now proposed by NICE) we are rendering our patients very susceptible to infection as we move on to the more intensive therapies - thus incurring extra anti-microbial costs.	Please refer to the Institute's statement on page one.
		4) Why FC? If one considers all haematological cancers showing a survival improvements this has been on the background of inducing a significantly higher complete remission rate than 70%-some would argue 90%. There are now several studies showing an overall survival advantage in	Please refer to the Institute's statement on page one.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		CLL patients if complete remission and minimal residual disease is achieved. With chlorambucil monotherapy only achieving a CR rate of 7% compared to FC 38% it is clear that chlorambucil will never lead to prolonged survival whereas at least FC is a step in the right direction. If chlorambucil and FC were both "new regimens" applying today for approval by NICE even allowing for the extra cost of fludarabine it is inconceivable that chlorambucil would be recommended ahead of FC. Would you honestly choose for yourself or your family such an inferior response rate? - that is what we as clinicians and patients are being asked to accept. I appreciate that NICE were not being asked to recommend FC and that the submission from Schering was for fludarabine monotherapy. I find it inconceivable however that the SMC can find a form of words to allow FC to be used and NICE cannot. It is in all our interests that NICE succeeds in it's role but the recommendation of a drug with only 7% CR rate is clearly wrong. Schering are partially responsible for this mess by not applying for consideration of FC combination therapy however it is NICE which stands to lose.	Please note that this does not imply a negative recommendation for the combination of fludarabine and cyclophosphamide.
NHS Professional 2		I would like to add my brief comments, from a personal and professional viewpoint. I have a large CLL clinic responsible for looking after several hundred patients with CLL from the catchment around the Leicester area, a population approaching a million people. I serve on the NCRI CLL clinical trials committee and as secretary to the UKCLL Forum. I have a strong clinical research interest in CLL in particular the role of antibody therapies in CLL. I ask for a reconsideration of the recommendations made by the ERG. Single agent therapy is seldom the treatment of choice in haematological malignancy. A research paper published in 1948 reported a small proportion of children receiving single agent chemotherapy enjoyed a temporary remission. At the time it was a breakthrough. Nowadays complex multi agent regimes are the norm and the majority of childhood leukaemia is cured. The situation is very different for therapy in CLL. NICE is limited technically to the submission of single agent fludarabine and no-one can yet claim that CLL is curable. However I do believe that my patients have a choice when it comes to their treatment. It is one of the tenets laid down in "good medical practice" to offer my patients the most effective therapy available. According to the current results of LRF CLL4 and many other similar trials the most effective combination therapy for CLL is purine analog based with cyclophosphamide (FC). FC with the addition of Rituximab or Mitoxantrone are also promising combinations with many	Comments noted. Comments noted. Comment noted. Please refer to the Institute's statement on page one.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		patients attaining a profound remission with no detectable disease (so called minimal residual diease or MRD)using the most sensitive techniques available - MRD negative CR	
		In my view the current treatment of choice for most patients with CLL is FC. Having wide experience with all the drug combinations for CLL, it is my experience that many patients into very old age can tolerate FC and it is often the more elderly patients who benefit the most as many do not require further therapy.	Please refer to the Institute's statement on page one.
		As clinicians we now have a wealth of knowledge regarding prognostic factors in CLL. Far from being a universally indolent disease of the very elderly CLL is a dangerous progressive disease of adulthood. Once a patient actually requires therapy median survival is closer to 5 or 6 years and in some of the worst prognostic groups an appalling overall survival of 2 or 3 years from diagnosis can be seen, which is worse than acute leukaemia in many cases. The division of patients into a good risk category of 25 years median survival for therapy purposes is meaningless as these non progressive stable patients will by definition not receive therapy anyway and whatever is recommended, these patients will never incur a cost. We can also identify patients who are likely to progress rapidly based on retrospective data from such studies as LRF CLL 4.	Comment noted.
		The technology to detect minimal residual disease is becoming increasingly accessible and is widely used. Prognostic factors are understood well enough to identify most of the poor risk and most of the good risk patients. Therapies exist which lead to complete remissions in most and deep MRD negative remissions in a proportion. My patients are fortunate enough to live in a wealthy first world country in the 21st century where the clinicians response to this remarkable convergence of diagnostic, therapeutic and prognostic technologies is to develop well thought out clinical trials. These trials should exist in a supportive NHS framework building from an evidence base and bolstered by NICE recommendations for future research.	Comment noted.
		In my view this means testing the prognostic factors prospectively in the context of the most effective therapy. One of the recommendations of the NICE committee was to consider the setting up of a trial to test which patients would respond best to single agent fludarabine retaining a chlorambucil control arm. As a practising clinician in the field of CLL, this makes no sense. No trial in the UK with such a design would accrue patients. I want my patients to receive combination therapy. I know FC works better and is cheaper than single agent fludarabine.	Comment noted.
		I ask therefore that the NICE committee reconsider in its conclusion, the role of combination FC therapy in CLL and make an amended recommendation that such a combination form the basis for future clinical trials in the UK rather than single agent fludarabine. The importance of the MRD negative complete remission as a step towards improving survival needs to be clarified and the	Please note that this does not imply a negative recommendation for the combination of fludarabine and cyclophosphamide.

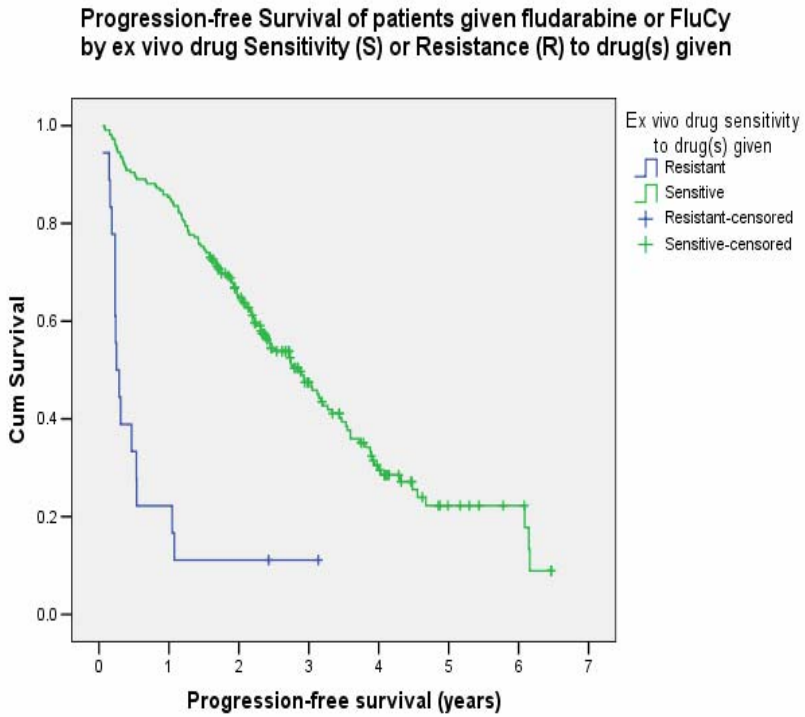
Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		role of prospectively testing biological prognostic factors needs further study.	
NHS Professional 3	1	I am surprised that no recommmendations can be made for fludarabine plus cyclophosphamide, given that evidence from 3 RCTs (MRC, ECOG, German) shows a consistent doubling of progression free survival compared with fludarabine monotherapy. While I agree that monotherapy offers only a modest improvement, this cannot be used as an argument against FC. I object the the phrase "and therefore...".	Please refer to the Institute's statement on page one.
	3	I am disappointed that the ECOG and German studies were not taken into account with respect to FC. These confirm the improvement in PFS (doubling) compared with fludarabine monotherapy. There was no chlorambucil arm in either of these studies, but this should not remove their relevance, since if we were to (wrongly) assume equivalence between flud and chlorambucil - a doubling of PFS for FC is still a strong argument.	Please refer to the Institute's statement on page one.
	4	I accept the argument for fludarabine monotherapy. There is no overall survival benefit, but given the disease trajectory for CLL and the fact patients receive many different therapies during, it will be difficult to demonstrate this in the future, and therefore this should not be used as an argument to negagate the importance of progression free survival.	Comment noted.
	6	The research agenda in CLL has moved on to the addition on monoclonals in first line phase 3 studies. I am disappointed that progression free survival has not be considered as a valuable endpoint with respect to FC.	Please refer to the Institute's statement on page one. In regards to progression free survival, as stated in FAD section 4.3 'the Committee heard from the clinical specialists about an agreement at an international workshop in chronic lymphocytic leukaemia (CLL) to use progression free survival as a surrogate marker for overall survival (in CLL). The Committee was persuaded that progression free survival is a meaningful clinical end point for CLL patients' (see FAD section 4.4).
	8	This should be reviewed as soon as practical with a view on a more detailed assessment of FC.	The Institute can only appraise fludarabine and cyclophosphamide combination therapy if it is instructed to do so by the Department of Health.
NHS Professional 4	1	The failure (inability) of NICE to review fludarabine plus cyclophosphamide (FC) creates a massive problem. It is clear that FC is the most effective therapy for patients with CLL who don"t	Please refer to the Institute's statement on page one.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		have any serious co-morbidity and will lead to a more expensive treatment approach. Failure to recommend FC will mean that patients will receive ineffective therapy. I strongly disagree with the guidance - it is a big retrograde step for patients with CLL.	
	2	In the LRF CLL4 autoimmune haemolytic anaemia was at least as common with chlorambucil therapy as fludarabine monotherapy. It appears from the LRF CLL4 trial and the equivalent German CLL Study Group Trial that FC is protective against the development of haemolytic anaemia compared to chlorambucil or fludarabine monotherapy.	Comment noted.
	3	It appears that, as expected FC, is more cost effective than fludarabine or chlorambucil	Comment noted.
	4	No ""CLL expert"" would argue with the statement about fludarabine monotherapy. However the FC combination is cost effective, results in significantly higher response rates and prolonged time to next treatment and is a major step forward in our treatment of CLL. FC will form the backbone of future combinations. The Committee is aware that it is almost universal that leukaemias and lymphomata are treated with combinations of between 2 and 8 different chemotherapeutic drugs. This is the only approach to improving survival for most of these maligancies. Not approving FC ignores this basic principles of oncology.	Please refer to the Institute's statement on page one.
	6	The LRF CLL4 trial, part of the NCRI portfolio, was the most effective CLL trial to be performed in the UK and arguably internationally. It addressed all of the above points in 777 patients. It is ridiculous, and probably unethical, to repeat this trial when we know the benefits of FC over fludarabine or chlorambucil. As the Chair of the NCRI CLL sub-group it is clear to me that this recommendation cannot be implemented.	The Committee has not recommended that the CLL4 trial should be repeated. Please refer to FAD section 6, were it is proposed that further evidence should be gathered but this does not refer to the CLL4 trial.
	7	I do not see the relation between advice on chronic myeloid leukaemia to this advice. They are very different disorders with very different therapies. A more related advice is on follicular lymphoma and diffuse large cell lymphoma which both recommend the combination chemotherapy approach.	This has been amended in the FAD.
NHS Professional 5	6.3	Your Appraisal Consultation Document 'Leukaemia (lymphocytic) – fludarabine' makes for interesting reading. One of the statements says: 6.3 The Committee recommended further research to identify prognostic markers that would allow better characterisation of subgroups of patients who will benefit the most from fludarabine. Much data to answer this has been generated by the LRF CLL4 trial but I can only assume that you were not presented with it. One of the key prognostic markers is Ex Vivo Drug Sensitivity. I sent you a document in June (attached again for easy reference) describing this.	Comments noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		Also attached are two graphs of Ex Vivo Drug Sensitivity data from CLL4. These initial results show that a subgroup of patients (18/237, 8%) characterised by ex vivo drug resistance to fludarabine +/- cyclophosphamide have very short (median 3 months) progression-free survival (PFS) compared with those that were drug sensitive (median PFS = 34.5 months) ($p<0.001$). This group of resistant patients also has poor survival (15.7 months) compared with 58.4 months for sensitive patients ($p=0.002$). Performing a test (that has already been shown to be cost-effective in CLL) so as to not treat patients resistant to fludarabine could improve the response rates, survival and cost-effectiveness of those that are treated with this drug. I believe that it will reflect badly on NICE if it does not take into consideration the latest research findings. Attached documents received: **Fludarabine as first-line treatment of chronic lymphocytic leukaemia: relevance of TRAC drug sensitivity assay** Submission to NICE. November 2006 Dr Andrew G Bosanquet PhD MRCPath FRSC, Director, Bath Cancer Research, Royal United Hospital, Bath Bath Cancer Research (BCR) has been investigating a test for cytotoxic drug sensitivity for over 20 years. The TRAC (Tumour Response to Anti-neoplastic Compounds) assay is a laboratory test in which malignant cells from a patient are incubated with cytotoxic drugs of relevance in treating their condition. It has been repeatedly shown that, in accordance with expectations, patients treated with test-sensitive drugs respond and survive better than patients treated with test-resistant drugs [Bosanquet, 1994]. BCR's focus has been on chronic lymphocytic leukaemia (CLL). We have had a particular interest in the relevance of testing for a patient's fludarabine sensitivity before treatment due to its efficacy in this disease. **Aim**. Our aim has been to determine to what extent treating on the basis of a TRAC result can improve patient response and survival. To this end, the efficacy of the TRAC assay is being tested in the second randomisation of the UK LRF CLL4 trial. **Methods**. BCR is both a research laboratory and a CPA (Clinical Pathology Accreditation) accredited laboratory providing the TRAC assay as a UK-wide service to haematologists. The	Comments noted.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		assay is a development of the DiSC (Differential Staining Cytotoxicity) assay [Bosanquet & Bell, 1996]. Leukaemic (mononuclear) cells are isolated from blood or other sources and incubated for 4 days with drugs. Cells are cytocentrifuged onto microscope slides, stained and their survival scored. A drug sensitivity index is determined for each drug such that 0% indicates greatest resistance to the drug and 100% the greatest sensitivity. **Results**. BCR has been testing fludarabine for nearly 20 years. In 1999 we published a follow-up of 243 CLL patients who had received chemotherapy after DiSC assay [Bosanquet et al, 1999]. Fludarabine-test-resistance was found in 12/100 (12%) of untreated patients and 45/143 (31%) of previously treated patients (including 17/32 (53%) of patients previously treated with fludarabine). Treating fludarabine-test-resistant patients with fludarabine resulted in poor response compared with fludarabine-test-sensitive patients (7% v 69%) and short survival (median 7.9 v 41.7 months; relative risk (RR) = 14.8; P < 0.0001). 81% of fludarabine-test-resistant patients were test sensitive to other CLL regimens. Of particular interest was that, if treated with chemotherapy **other** than fludarabine, fludarabine-test-resistant patients responded better and survived substantially longer than if they were treated with fludarabine (RR = 2.9; P = 0.001). In 1999, the results of an economic assessment of the test, performed by the Centre for Health Economics, University of York, were published. It concluded "the results suggest that in vitro drug sensitivity is an important independent prognostic variable to include in future trials, and that the DiSC assay may be a cost-effective use of health resources: the estimated incremental cost-effectiveness was £1,470 per life-year gained" [Mason et al, 1999]. In early results from the CLL4 trial, 8% of untreated patients were found to be test-resistant to fludarabine or fludarabine-cyclophosphamide. 194 of 214 (91%) of test-sensitive patients subsequently given these fludarabine regimes responded whilst only 4 of 18 (22%) test-resistant patients responded (p < 0.00001) [Bosanquet et al, 2006]. **Conclusions**. • Fludarabine-test-resistance has been found to be a powerful independent prognostic factor. • Fludarabine-test-resistance could be used to identify patients who might obtain greater benefit from other chemotherapy regimens. • Test results could be a cost-effective use of health resources. **References** (links to abstracts provided, visit http://caltri.org/publications.htm for pdfs of some papers) Bosanquet AG. Forum Trends in Experimental and Clinical Medicine 4.2 (1994): 179-98. Abstract Bosanquet AG, PB Bell. Leukaemia Research 20.2 (1996): 143-53. Abstract	

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		Bosanquet AG, et al. British Journal of Haematology 106 (1999): 71-77. Abstract Mason JM, et al. International Journal of Technology & Assessment in Health Care 15 (1999): 173-184. Abstract Bosanquet AG, et al. Haematologica / The Hematology Journal 91 (Suppl. 1) (2006): 100 (Abstract #267).	

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		Fludarabine ex vivo drug sensitivity survivals from CLL4 – Preliminary results  	

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		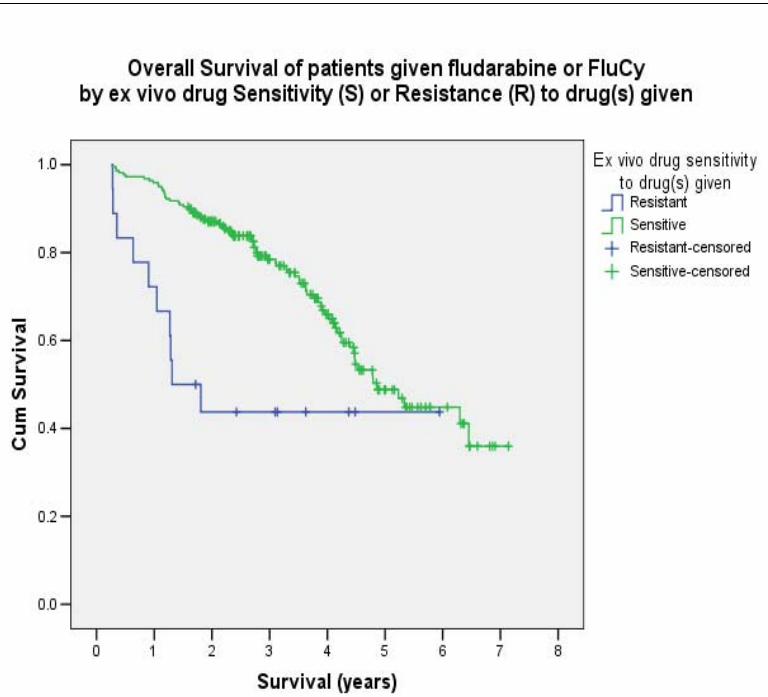	
Other 1	3	No consideration seems to have been taken of the Cochrane review on fludarabine: Steurer M, Pall G, Richards S, Schwarzer G, Bohlius J, Greil R. Purine Antagonists for Chronic Lymphocytic Leukaemia. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004270. DOI: 10.1002/14651858.CD004270.pub2.	The search strategy for the manufacturer's systematic review covered the time period 1950 to January 2006. The named study was excluded in the manufacturer's submission as only a protocol for the RCT was available up to January 2006. The Cochrane review for 'Purine Antagonists for Chronic Lymphocytic Leukaemia' was published online on the 19th July 2006 and was therefore not available for the Committees deliberations on this appraisal.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
Patient 1		I understand from contacts at the Institute of Cancer Research that NICE intends to rule out the combination of Fludarabine and cyclophosphamide (FC) as a first-line treatment for chronic lymphocytic leukaemia (CLL). I should like to give you my personal experience as a patient of this treatment to try to persuade you to reconsider. In August 2001 I was diagnosed with CLL and became too unwell to continue working as a teacher of A-level physics and further mathematics or to chair tribunals in the Magistrates' Court. In May 2002 I began 6 courses of FC and obtained a nodular partial remission. By May 2003 I was well enough to return to my duties as a magistrate and in January 2004 to resume teaching maths and physics. Since then my health has been extremely good. Just over 4½ years since start of treatment I have high energy levels and have missed only 2 or 3 days of teaching in total, due to minor winter ailments. My most recent blood counts (haemoglobin, neutrophils, platelets, lymphocytes etc.) were all within the normal range, with just 2% residual disease. Two years ago I gave away my car and I make all local journeys by bicycle. The last two summer holidays have involved bicycle rides of more than 300 miles each. I understand that the standard treatment for CLL (chlorambucil) would be unlikely to have produced this quality and length of remission. During the period when I was ill, I received incapacity benefit. But since resuming work I have paid income tax and national insurance, supplied a shortage skill as a further maths and physics teacher and contributed roughly 40 days per year to HM Court Service as a magistrate. It occurs to me therefore that, in my case at least, the additional cost of FC over chlorambucil will have been enormously outweighed by my not needing further treatment, ceasing to claim incapacity benefit, paying income tax and national insurance and contributing specialist experience and skills. I should therefore like to urge you to reconsider the FC treatment as first-line treatment for CLL in order to help younger sufferers (I was aged 58 at diagnosis) to regain an active and productive life, contributing to the national Exchequer and probably saving the NHS money in drug prescriptions and hospital admissions.	The Institute would like to thank you for your comments about your own personal experience of treatment using fludarabine and cyclophosphamide combination therapy. Please refer to the Institute's statement on page one.