**TITLE: Guideline for the Treatment of Chronic Lymphocytic Leukaemia**

**A British Society for Haematology Guideline**

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**Methodology**

This guideline was compiled according to the British Society Haematology (BSH) process at http://www.b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at <http://www.gradeworkinggroup.org>.

The guideline group was selected to be representative of UK medical experts and patients. Recommendations are based on a review of the literature using Medline/Pubmed searches under the heading, chronic lymphocytic leukaemia AND phase III AND (Ibrutinib OR Idelalisib OR Venetoclax OR Obinutuzumab OR Ofatumumab OR Bendamustine OR Rituximab OR Fludarabine OR Cyclophosphamide OR Chlorambucil). Only English language publications from 1st August 2011 to 31st March 2017 were included in the literature search. Titles and/or abstracts of publications obtained from the database searches described were manually reviewed.

The writing group produced the draft guideline, revised by members of the UK CLL Forum Executive, including patient representatives of the CLL Support Association and Leukaemia Care. The manuscript was reviewed by the BSH Haemato-Oncology Taskforce, and approved by the BSH guidelines executive committee.

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia. In all cases individual patient circumstances may dictate an alternative approach.

**Introduction**

The significant developments in the treatment of Chronic Lymphocytic Leukaemia (CLL) in recent years demand an update of the BCSH Guidelines for CLL ([Oscier, Dearden et al. 2012](#_ENREF_89)) with a focus on therapy. The guidance in this document refers to treatment outside clinical trials. However, the basic principal remains that wherever possible, treatment of patients with CLL should be delivered within the context of a clinical trial.

**Initial approach to patient management**

CLL is a chronically relapsing and remitting leukaemia. It is therefore particularly important that patients are able to establish trust with the clinician managing their disease over years. The diagnosis is often overwhelming for patients and their families and it can be difficult for the patient to understand the complexities of treatments and the concept of 'watch and wait'. Patients will expect and are entitled to be honestly informed about their disease. The majority of patients benefit from, and should be offered, information about CLL. All patients should be supported by a Clinical Nurse Specialist with experience in CLL. The national patient support associations are also a valuable resource for patients and have internet sites and booklets with reliable information ([CLLSA 2015](#_ENREF_18), [Bloodwise 2017](#_ENREF_7), [LeukaemiaCare 2017](#_ENREF_70), [Macmillan 2017](#_ENREF_73)).

**Clinical assessment prior to treatment**

Any treatment decision has to take into account the wishes of the patient and the desired treatment outcome (disease control or remission induction). The indications for treatment of CLL patients are outlined in the International Working Group CLL (IWCLL) criteria and include progressive lymphadenopathy, hepatosplenomegaly and/or splenomegaly, deteriorating blood counts and constitutional symptoms ([Hallek, Cheson et al. 2008](#_ENREF_49), [Hallek 2017](#_ENREF_48)).

The expertise of the clinician, the performance status of the patient and characteristics of disease biology are important determinants of outcome even for patients receiving identical therapy ([Shanafelt, Kay et al. 2012](#_ENREF_99), [Goede, Cramer et al. 2014](#_ENREF_42)).

Given that almost 90% of CLL patients have one or more co-morbidities, the potential risks and benefits of a particular treatment need to be fully assessed in each individual patient by an experienced CLL clinician and discussed at the multi-disciplinary team (MDT) meeting ([Thurmes, Call et al. 2008](#_ENREF_106)).

The optimal strategy to determine fitness for chemotherapy remains undetermined and there is no agreement on the use of a specific, formal co-morbidity assessment tool. Poor performance status might be disease-related and should not lead per se to a reduction of therapy-intensity, especially not in patients with rapidly progressing disease.

In the relapsed/refractory setting, the choice of approved targeted agent might depend on their respective specific toxicity profile (i.e. anticoagulation, cardiac history, etc.).

Pre-treatment assessment of disease status (eg. role of bone marrow assessment, CT scans) remains as per current guideline ([Oscier, Dearden et al. 2012](#_ENREF_89)).

**Molecular assessment prior to treatment**

As chemoimmunotherapy is ineffective in patients with *TP53* disruption and alternative agents are available, it is essential that all patients are tested for the presence of both deletions AND mutations of *TP53* before each line of therapy ([Furman, Sharman et al. 2014](#_ENREF_36), [Farooqui, Valdez et al. 2015](#_ENREF_30), [Rossi, Terzi-di-Bergamo et al. 2015](#_ENREF_95), [Roberts, Davids et al. 2016](#_ENREF_92)). As small *TP53* disrupted subclones have been shown to impact on clinical outcome ([Rossi, Rasi et al. 2013](#_ENREF_94), [Landau, Tausch et al. 2015](#_ENREF_68), [Nadeu, Delgado et al. 2016](#_ENREF_86)), the results of *TP53* testing should be interpreted in light of the sensitivity of the diagnostic methodologies used. The definition of test sensitivity should always be established as part of the clinical laboratory accreditation process and sensitivity thresholds should be included in the diagnostic report.

Retrospective studies have suggested that the sub-group of patients with mutated *IGHV* genes experience prolonged remissions with chemoimmunotherapy ([Lucas, Ruppert et al. 2015](#_ENREF_72), [Fischer, Bahlo et al. 2016](#_ENREF_32), [Thompson, Tam et al. 2016](#_ENREF_105)). While these results require independent validation, testing for *IGHV* mutation status should be considered for patients eligible to receive chemoimmunotherapy to provide information for the likelihood of long-term progression-free-survival following chemoimmunotherapy ([Rossi, Terzi-di-Bergamo et al. 2015](#_ENREF_95), [Fischer, Bahlo et al. 2016](#_ENREF_32)).

**Recommendations**

* **Treatment choice and aims should be decided in discussion with the patient and a CLL expert (GRADE III) and are based on the patient’s wishes, co-morbidities and potential drug side-effects (GRADE IV)**
* **All patients should be offered the opportunity to participate in a clinical trial, where available.**
* **Tests for *TP53* disruption should be performed on all patients prior to each line of therapy, should include both mutation and deletion detection (GRADE IB) and ideally should also reveal subclonal *TP53* mutations**
* **Analysis of the *IGHV* mutation status should also be considered (GRADE III)**

**Front-line therapy**

**Initial treatment of fit patients without *TP53* disruption**

The pivotal German CLL8 study showed that the addition of rituximab (R) to the chemotherapy backbone (fludarabine and cyclophosphamide (FC) improved not just progression free (PFS) survival but also overall survival (OS) of fit patients with CLL ([Hallek, Fischer et al. 2010](#_ENREF_50)). Subsequently, both the UK’s ARCTIC and ADMIRE trials ([Howard, Munir et al. 2017](#_ENREF_55), [Munir, Howard et al. 2017](#_ENREF_85)) and the German CLL10 trial ([Eichhorst, Fink et al. 2016](#_ENREF_29)) provided further evidence that FCR remains the treatment of choice for fit patients.

In addition, ARCTIC, ADMIRE and the Cancer Trials Ireland studies demonstrated that rituximab with oral administration of FC yields high rates of response and rates of Minimal Residual Disease (MRD)-negativity compared to historical series using intravenous FC ([Appleby, O'Brien et al. 2017](#_ENREF_3), [Howard, Munir et al. 2017](#_ENREF_55), [Munir, Howard et al. 2017](#_ENREF_85)).

In the German CLL10 trial comparing FCR x 6 versus bendamustine with rituximab (BR) x 6, FCR proved superior in terms of overall response rate (ORR), achievement of MRD-negative remissions and duration of first remission in young fit patients. Although the BR arm of the trial had a statistically higher proportion of older and *IGHV* unmutated patients, patients in the FCR arm experienced more serious adverse events (SAE), particularly neutropenia and serious infections. OS remains similar in both arms. A retrospective sub-group analysis of the trial suggested that elderly patients (>65 years old) are more likely to experience toxicity with intensive therapy, and current US National Cancer Control Network guidelines do not recommend fludarabine for patients aged >70 years ([Wierda, Zelenetz et al. 2017](#_ENREF_111)). However, there is no international consensus on a specific age restriction for fludarabine-based chemotherapy ([Martell, Peterson et al. 2002](#_ENREF_75), [Michallet, Cazin et al. 2013](#_ENREF_81)).

**Recommendation**

* **Fludarabine, Cyclophosphamide and Rituximab (FCR) is recommended as initial therapy for previously untreated fit patients without *TP53* disruption outside clinical trials and is NICE approved (GRADE IB)**
* **Bendamustine and Rituximab (BR) is an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions e.g renal impairment, more advanced age, concerns with marrow capacity or patient preference (GRADE III)**

**Front-line treatment of less fit patients with CLL**

Due to the age distribution of CLL, two-thirds of patients are likely to have at least one significant co-morbidity and higher risk disease ([Truger, Jeromin et al. 2015](#_ENREF_107)). The considerable clinical heterogeneity seen between patients should be considered when planning treatment ([Goede and Hallek 2011](#_ENREF_44)). Co-morbidity scores such as the Cumulative Illness Rating Scale (CIRS) ([Linn, Linn et al. 1968](#_ENREF_71), [Baumann, Delgado et al. 2014](#_ENREF_6)) are not routinely recommended, but have been used in clinical trials to objectively define fitness. As with fit patients, testing for *TP53* deletions and mutations should be standard practice.

Two major randomised clinical trials, GCLLSG CLL11 and COMPLEMENT-1 included older patients and patients with significant co-morbidities and led to approval of combinations of chlorambucil (Clb) with obinutuzumab (Obin) or ofatumumab (Ofa), respectively ([Goede, Fischer et al. 2014](#_ENREF_43), [Lee, Miller et al. 2014](#_ENREF_69), [Hillmen, Robak et al. 2015](#_ENREF_53)). In addition to demonstrating the superiority of Clb-R over Clb alone, the CLL11 study confirmed a significant PFS and time to next treatment (TTNT) benefit with Clb-obinutuzumab (Clb-Obin) over Clb-R and an OS benefit compared to Clb. Of note, the lower limit of creatinine clearance permitted was 30ml/min. Infusional reactions (IR) with obinutuzumab, although manageable, were significantly higher than with rituximab (grade 3-4 IR 20% vs 4%) ([Goede, Fischer et al. 2014](#_ENREF_43), [Goede, Klein et al. 2015](#_ENREF_45)). The COMPLEMENT-1 study demonstrated a significantly prolonged PFS with Clb-Ofa compared to Clb alone, but no difference in OS. Grade 3-4 IRs were reported at 10% with Ofatumumab ([Hillmen, Robak et al. 2015](#_ENREF_53)). Comparison between the two studies is hampered amongst other factors by differences in the dose and schedule of Clb (0.5mg/kg on days 1+15 in CLL11 and 10mg/m2 days 1-7 in COMPLEMENT-1).

A randomised comparison of BR with Clb-R for fludarabine-ineligible treatment-naïve patients showed a complete response rate after Cycle 6 of 24% versus 9%; respectively (*P*=0.002) and a median of 40 months versus 30 months (*P*=0.003). Overall response rate and OS were not different. In first-line patients with a complete response, MRD-negativity was higher with BR than Clb-R (66% *vs.* 36%).([Michallet, Aktan et al. 2015](#_ENREF_80), [Michallet, Aktan et al. 2018](#_ENREF_79)). Clb-R is not routinely recommended as two randomised trials showed inferior PFS compared to either BR or Clb-Obin.

Ibrutinib is licensed for front-line use in patients without *TP53* disruption as excellent responses and a significant improvement in OS were demonstrated compared to Clb in a randomised phase 3 study of older patients without *TP53* deletion (RESONATE-2) ([Burger, Tedeschi et al. 2015](#_ENREF_11)).

**Recommendation**

* **Chlorambucil-Obinutuzumab or Chlorambucil-Ofatumumab combinations are NICE approved and are the current standard of care in less fit patients (GRADE IB)**
* **Bendamustine-Rituximab might be considered as an alternative. (GRADE IB)**
* **Chlorambucil in combination with Rituximab is not routinely recommended (GRADE IB)**
* **Ibrutinib is an acceptable treatment option, but not NICE approved in this indication (GRADE IB)**

**Treatment of extremely frail patients**

While extremely frail patients may tolerate mild oral chemotherapy (chlorambucil), they may find additional antibody therapy unacceptable, with the requirement for intravenous infusions and more frequent hospital attendance. Best supportive care was recommended for this group before the advent of B-cell receptor signalling pathway inhibitors (BCRi), preserving quality of life and concentrating on infection prevention, pain management, and transfusion support. The introduction of non-chemotherapy agents has expanded options for extremely frail patients: the newer therapies are more effective, have a different side-effect profile from chemotherapy and are administered orally.

However, all clinical trials have excluded very frail patients because of performance status, number of co-morbitidies and/or renal function and therefore there is no evidence on how to manage CLL in extremely frail patients.

As with all patients, the goal of treatment in this group should be determined in discussion with each patient. Extremely frail patients could be offered a brief trial of treatment that includes clear guidance on when to stop, and should be very closely monitored.

**Recommendation**

* **Single agent chlorambucil may be used in patients who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable (GRADE IV)**
* **Corticosteroid monotherapy can be considered (GRADE IV)**
* **Rituximab monotherapy is not recommended (GRADE IV)**
* **Utility and side-effect profiles of BCRi in extremely frail patients have not been evaluated in clinical trials and BCRi are not NICE approved in front-line therapy of standard risk CLL (GRADE IV)**

**Treatment of patients with *TP53* disruption (deletions and/or mutations)**

A minority of patients (5-10%) will have evidence of *TP53* disruption at time of first treatment. 4% of cases are identified by FISH for deletions of chromosome 17p. Using Sanger sequencing, an additional 4-6% of patients carry mutations in *TP53*. This percentage increases further when using more sensitive next generation sequencing. Treatment of *TP53* disrupted patients with standard chemotherapy is associated with significantly inferior disease response, duration of response and OS compared with patients who do not have *TP53* disruption ([Dohner, Stilgenbauer et al. 2000](#_ENREF_24), [Tam, Wierda et al. 2008](#_ENREF_104), [Zenz, Mertens et al. 2008](#_ENREF_116)).

Compelling data has been published on the treatment of patients with *TP53* disruption with BCRi, namely idelalisib with rituximab or ibrutinib monotherapy, or the BCL-2 inhibitor venetoclax ([Furman, Sharman et al. 2014](#_ENREF_36), [Farooqui, Valdez et al. 2015](#_ENREF_30), [O'Brien, Jones et al. 2016](#_ENREF_88), [Stilgenbauer, Eichhorst et al. 2016](#_ENREF_102)). Although the majority of *TP53* disrupted patients in these studies were treated at relapse, similarly high ORR and superior PFS were observed in the few patients with *TP53* disrupted CLL treated in front-line. These favourable outcomes led to the current licensing of these drugs for front-line treatment of *TP53*-disrupted CLL, and to subsequent NICE approval of ibrutinib monotherapy and idelalisib with rituximab for this indication. However, ongoing pharmacovigilance revealed a higher risk of infection and death with idelalisib therapy than previously noted ([Lampson, Kasar et al. 2016](#_ENREF_67)), leading to the European Medicine Agency (EMA) to review its license for idelalisib, and to recommend idelalisib for “first-line treatment of CLL in the presence of 17p deletion or *TP53* mutation in patients who are not eligible for any other therapies”. The same guidance also recommended that all patient should undergo regular cytomegalovirus (CMV) monitoring and pneumocystis jiroveci (PJP) prophylaxis.

**Recommendation**

* **Ibrutinib is the treatment of choice in front-line therapy for patients with *TP53* disruption and is now NICE approved (GRADE IB)**
* **Idelalisib and rituximab combination therapy is a suitable alternative for patients for whom ibrutinib is deemed inappropriate such as patients with significant cardiac disease or patients receiving vitamin K antagonists, and is also NICE approved (GRADE IB)**

**Maintenance therapy**

Two prospective randomised trials of anti-CD20 antibody maintenance therapy in CLL have been published ([Abrisqueta, Villamor et al. 2013](#_ENREF_2), [Greil, Obrtlikova et al. 2016](#_ENREF_46)). Lenalidomide maintenance has been studied following FCR and other chemoimmunotherapy regimes ([Egle, Steurer et al. 2011](#_ENREF_28), [Fink, Bahlo et al. 2016](#_ENREF_31), [Foa, Schuh et al. 2016](#_ENREF_34)). The data suggest that patients on maintenance therapy may benefit in terms of PFS, but no OS advantage has been presented. There remain concerns with regards to potential toxicity of maintenance therapy in CLL and further follow-up and analysis of these trials are required. At present, maintenance therapy cannot be recommended in CLL.

**Recommendation**

**• Consolidation and maintenance therapy is not routinely recommended in CLL as it is unclear to what extent the PFS benefit is offset by long-term toxicity (GRADE IB)**

**Management of relapsed or refractory CLL**

As for front-line therapy, the criteria for treatment remain as defined by the IWCLL 2008 guidelines ([Hallek, Cheson et al. 2008](#_ENREF_49)). Many patients with relapsed but asymptomatic CLL can be monitored with no therapy for a period of time. At the time of treatment re-initiation, testing for the presence of *TP53* disruption by FISH and DNA sequencing should be repeated. Chemoimmunotherapy is not advised in patients who have not responded to prior chemoimmunotherapy, relapse within 36 months of chemoimmunotherapy or have acquired *TP53* disruption. In addition, many patients who achieved long remissions with front-line chemoimmunotherapy acquire co-morbidities making them ineligible for further chemoimmunotherapy. Based on randomised trials in these patient populations showing significant gains in OS compared to single-agent anti-CD20, licensed treatment options include ibrutinib monotherapy (or in combination with bendamustine and rituximab) or idelalisib in combination with either rituximab or ofatumumab ([Byrd, Brown et al. 2014](#_ENREF_12), [Furman, Sharman et al. 2014](#_ENREF_36), [Chanan-Khan, Cramer et al. 2016](#_ENREF_15), [Jones, Robak et al. 2017](#_ENREF_62), [Zelenetz, Barrientos et al. 2017](#_ENREF_114)).

Deciding whether ibrutinib or idelalisib with rituximab is most appropriate for an individual patient depends on a range of factors including toxicity profile and convenience of delivery. The value of adding bendamustine to either ibrutinib or idelalisib plus rituximab is unclear, since the median PFS was similar for the respective BCRi with or without the addition of bendamustine.

Of note, patients who were less heavily pre-treated, or who had experienced a prolonged first remission with chemoimmunotherapy were excluded from randomised trials of both BCRis. Furthermore, neither ibrutinib nor idelalisib plus rituximab have been evaluated prospectively against chemoimmunotherapy in the relapse setting.

The consideration to treat relapse with chemoimmunotherapy depends on (1) the time to relapse, (2) the type of frontline therapy and (3) the absence of *TP53* disruption. In LUCID, REACH and MDACC single centre series patients were FCR naïve and received FC, FCR, FCLR at relapse leading to a median PFS of 20-30 months ([Robak, Dmoszynska et al. 2010](#_ENREF_91), [Badoux, Keating et al. 2011](#_ENREF_5), [Awan, Hillmen et al. 2014](#_ENREF_4)). MDACC and French Collaborative groups included only patients with prior exposure to FCR ([Tam, O'Brien et al. 2014](#_ENREF_103), [Fornecker, Aurran-Schleinitz et al. 2015](#_ENREF_35)). Treatment was more heterogenous (FCR, BR, alemtuzumab, CHOP-R etc), but the median PFS was under 2 years. Re-treatment with CIT may be more effective in those patients with long initial remissions ([Badoux, Keating et al. 2011](#_ENREF_5), [Fischer, Cramer et al. 2011](#_ENREF_33), [Tam, O'Brien et al. 2014](#_ENREF_103)). The strongest evidence for BR in the relapsed/refractory setting comes from the control arms of both the HELIOS and Gilead 115 studies showing similar PFS of approximately one year to the phase II study of Fischer et al. ([Fischer, Cramer et al. 2011](#_ENREF_33), [Chanan-Khan, Cramer et al. 2016](#_ENREF_15), [Zelenetz, Barrientos et al. 2017](#_ENREF_114)).

There is limited data on patients who progress on BCRi including patients with *TP53* disruption. It is important to recognize that an increase in peripheral lymphocytosis represents response to the new agents and NOT disease progression. For those patients who genuinely progress on BCRi, a number of observational studies indicate a poor outcome in the absence of alternative treatment ([Maddocks, Ruppert et al. 2015](#_ENREF_74), [UKCLLForum 2016](#_ENREF_108), [Jain, Thompson et al. 2017](#_ENREF_57)). Real-world case studies of patients who progressed on one BCRi and were switched to an alternative targeted agent suggest a short PFS ([Mato, Nabhan et al. 2016](#_ENREF_77)). A phase II study and a large real-world data collection of patients who progressed on either ibrutinib or idelalisib ([Jones, Choi et al. 2016](#_ENREF_61), [Mato, Nabhan et al. 2016](#_ENREF_77), [Mato, Hill et al. 2017](#_ENREF_76)) shows efficacy of venetoclax in this setting, which is also highly efficacious in *TP53* disrupted disease ([Stilgenbauer, Eichhorst et al. 2016](#_ENREF_102)). Venetoclax is now licensed for use in patients with CLL who have failed or are unsuitable for BCRi therapy and either have a *TP53* disruption or a history of failing prior chemoimmunotherapy.

The benefit of venetoclax in combination with rituximab (VR) over bendamustine plus rituximab (BR) for patients with relapsed/refractory CLL was recently demonstrated by the MURANO study showing impressive independent review committee-assessed PFS (HR, 0.19; 95% CI, 0.13 to 0.28; P<0.0001) and greater proportion of VR-treated patients attaining peripheral blood MRD-negativity (83.5% vs. 23.1%)([Seymour, Kipps et al. 2018](#_ENREF_98)). Although follow-up of the study is short, this suggests that the combination of venetoclax with rituximab is likely to become a third option for treating relapsed/refractory CLL. Only 5 of the 389 patients entered into the study were previously exposed to BCRi.

**Recommendation**

* **Idelalisib with rituximab, or ibrutinib monotherapy, are the treatments of choice for patients with CLL who are refractory to chemo-immunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate. In England, for both ibrutinib monotherapy and idelalisib with rituximab, patients need to meet specific NICE criteria based on the respective clinical trial inclusion criteria – see appendix 1 (GRADE IB).**
* **The addition of bendamustine to these BCRis is not recommended (GRADE IV).**
* **Venetoclax in combination with rituximab might also become an option for BCRi naïve patients (Grade IB).**
* **Re-treatment with chemoimmunotherapy may be considered as an option for fit patients with CLL who relapse after a prolonged remission (GRADE III)**
* **Venetoclax is the treatment of choice for patients who fail BCRi therapy and is currently funded through the NHSE Cancer Drugs Fund (GRADE III).**

**Response Assessment in the Era of Novel Therapies**

The IWCLL guidelines on diagnosis and treatment of CLL ([Hallek, Cheson et al. 2008](#_ENREF_49)), contain widely used, firmly established response criteria, developed in the era of conventional chemotherapy. Rigorous application of these criteria, however, may not always be appropriate in the era of novel therapies.

Patients receiving BCRi often have a brisk improvement in lymphadenopathy, splenomegaly and constitutional symptoms upon initiation of therapy, but a surge in peripheral lymphocytosis due to redistribution of lymphocytes from tissues ([Byrd, Furman et al. 2013](#_ENREF_14), [Brown, Byrd et al. 2014](#_ENREF_9), [Wodarz, Garg et al. 2014](#_ENREF_113)) that can persist for over a year. The IWCLL issued an amendment to its guidelines which recognise that an increase in lymphocytosis is a feature of BCRi and in isolation does not represent Progressive Disease. An updated category of response called “partial remission with lymphocytosis” was therefore created ([Hallek 2012](#_ENREF_47)).

Moreover, and in line with developments in solid tumour oncology, an updated set of ‘Immune Response Criteria’ was recently proposed by Cheson et. al. for assessment of haematology patients receiving novel agents, the provisional ‘Lymphoma Response to Immunomodulatory Criteria ‘LyRIC’ criteria ([Cheson, Ansell et al. 2016](#_ENREF_17)). LyRIC includes an additional response category, named ‘indeterminate response’. This provisional category recognises that in the era of novel agents, modifications to conventional response assessment criteria are needed if patients are not to be incorrectly defined as having a suboptimal response to therapy, and risk inappropriate early treatment withdrawal.

**Recommendation**

* **Clinicians should recognize “partial remission with lymphocytosis” and “indeterminate response” when treating patients with CLL in the era of novel agents (GRADE IB)**
* **In patients who are otherwise gaining apparent clinical benefit, clinicians should avoid early withdrawal of BCRi (GRADE IB)**

**The role of Allogeneic stem cell transplantation**

Allogeneic stem cell transplantation (alloSCT) was previously considered as the standard of care for selected patients with refractory disease as defined by response to purine analogue based therapy of less than 6 months, *TP53* disruption or high-grade transformation and can effectively deliver durable remission in patients with otherwise high-risk disease ([BSBMT 2013](#_ENREF_10)). The decision to transplant should be based on remission status, patient age, performance status, co-morbidity and patient preference, donor status and availability of alternative treatments. In the event of disease progression on current therapy, early discussion with a transplant centre is recommended ([Dreger, Montserrat et al. 2015](#_ENREF_25)). The efficacy of alloSCT is highest in patients with good performance status, no significant co-morbidity, a HLA matched sibling donor and non-bulky disease at the time of transplant. However, alloSCT is associated with short and long-term toxicity ([Dreger, Schetelig et al. 2014](#_ENREF_26), [Kramer, Stilgenbauer et al. 2017](#_ENREF_66), [van Gelder, Ziagkos et al. 2017](#_ENREF_109)). The demographics of CLL limits the applicability of transplantation in most patients and its role in the management of CLL has more recently been brought into question with the advent of new targeted therapies ([Dreger, Montserrat et al. 2015](#_ENREF_25)). Although patients with relapsed CLL and *TP53* disruption benefit significantly from BCRi compared to historical data, most patients relapse within 3 years ([Sharman, Coutre et al. 2014](#_ENREF_100), [Byrd, Furman et al. 2015](#_ENREF_13), [O'Brien, Jones et al. 2016](#_ENREF_88), [Schetelig, de Wreede et al. 2017](#_ENREF_97)) and the optimal treatment for patients who fail BCRi is uncertain. For patients with Richter transformation at any stage, prognosis remains very poor and alloSCT remains the standard of care for patients achieving remission to induction chemotherapy ([Kharfan-Dabaja, Kumar et al. 2016](#_ENREF_65)).

**Recommendation**

* **AlloSCT is a treatment option for patients with CLL who have either**
	+ **failed chemoimmunotherapy and BCRi therapy irrespective of TP53 status**
	+ **harbour a *TP53* disruption and have not responded or lost response to BCRi therapy (GRADE III)**
* **AlloSCT should be considered for all eligible patients with Richter transformation (GRADE III)**

**Supportive care in CLL**

**Infection**

CLL is characterised by gradual reduction in humoral immunity and the development of hypogammaglobulinaemia ([Ravandi and O'Brien 2006](#_ENREF_90), [Morrison 2010](#_ENREF_84)). This can be exacerbated by intermittent chemoimmunotherapy ([Hensel, Kornacker et al. 2003](#_ENREF_51)). In addition, many treatment regimens are associated with CD4 T-cell lymphopenia ([Gassner, Weiss et al. 2011](#_ENREF_38), [Garcia Munoz, Izquierdo-Gil et al. 2014](#_ENREF_37)) and CD4 counts <0.2 x 109/L are significantly associated with opportunistic infections.

All patients should be screened for evidence of prior hepatitis B or C infection prior to therapy. Reactivation of viral hepatitis has been described following fludarabine, bendamustine, anti-CD20 therapy and, BTKi ([Coluccio, Begini et al. 2017](#_ENREF_19), [Herishanu, Katchman et al. 2017](#_ENREF_52)). CLL patients with evidence of prior infection should be managed jointly with a specialist hepatologist ([Hallek, Cheson et al. 2008](#_ENREF_49), [Hwang, Somerfield et al. 2015](#_ENREF_56)).

Hypogammaglobulinaemia and recurrent infection can exacerbate underlying co-morbidities and may lead to structural lung disease such as bronchiectasis ([Curtin, Webster et al. 1991](#_ENREF_21), [Gharagozlou, Ebrahimi et al. 2006](#_ENREF_39)). However, in 79% of CLL patients with normal IgG concentrations, suboptimal antibody responses to commonly encountered bacteria can be found (Parry, Birtwistle et al. 2015).

Strategies to reduce this risk include vaccination, antibiotic prophylaxis, early pre-emptive antimicrobial therapy and immunoglobulin replacement therapy ([Egerer, Hensel et al. 2001](#_ENREF_27)).

Patients with CLL should be offered vaccination against seasonal Influenza and pneumococcal disease ([Rubin, Levin et al. 2014](#_ENREF_96), [Wierda, Zelenetz et al. 2017](#_ENREF_111)).

The Department of Health and the Joint Committee on Vaccination and Immunisation issued specific recommendations on additional vaccination for patients at increased risk of mortality from invasive pneumococcal disease, including CLL patients. Vaccination with pneumococcal conjugate vaccine (PCV13, Prenvar®) is recommended for all CLL patients, followed by PPV23 (Pneumovax II®) at least two months later (irrespective of previous pneumococcal vaccinations)([JCVI 2013](#_ENREF_59), [JCVI 2015](#_ENREF_60), [DOH 2017](#_ENREF_23)).

However, many patients, even with early stage CLL are unable to mount a dynamic response to vaccination (Ljungman, Nahi et al. 2005).

Current guidelines concerning use of immunoglobulin replacement stipulate that patients with CLL should have documented failure to respond to vaccination and breakthrough infections on prophylactic antibiotic ([Wimperis 2011](#_ENREF_112)). This highlights the need to vaccinate early and document dynamic response to pneumococcal vaccination.

In line with the previous guidelines, live vaccinations such as polio, herpes zoster and yellow fever are not recommended.

**Recommendation**

* **All patients with CLL should be offered seasonal Influenza vaccination.**
* **All patients with CLL should be offered pneumococcal vaccination in the form of pneumococcal conjugate vaccine (PCV13 or Prenvar 13®) followed by pneumococcal polysaccharide vaccine (PPV23 or Pneumovax®), at least two months later (UK Department of Health Guidance)**
* **Assessment of response to pneumococcal vaccination is indicated in all patients with symptomatic secondary immunodeficiency to accelerate access to immunoglobulin replacement therapy (GRADE IV)**
* **Patients with reduced IgG <5g/L and recurrent infections who have failed a 6 months’ trial of broad spectrum prophylactic antibiotic (according to local antimicrobiobial protocols) should be offered immunoglobulin replacement therapy (GRADE IV)**
* **Prophylactic cotrimoxazole or nebulised pentamidine can reduce the risk of Pneumocystis jirovecii (PJP) while prophylactic aciclovir may reduce risk of herpes zoster reactivation (GRADE IV)**

**Management of side-effects during targeted therapy**

The increasingly widespread availability and continuous use of targeted agents has led to a growing cohort of patients who, while no longer subject to the volatility associated with intermittent cytoreductive agents, may experience complications of on-going secondary immunodeficiency and treatment related side-effects (for a full list of side-effects and drug interactions, please refer to ([AbbVie 2017](#_ENREF_1), [Gilead 2017](#_ENREF_40), [Janssen-Cilag 2017](#_ENREF_58))). Physicians must maintain good pharmacovigilance and encourage patients to discuss any new medication to prevent unforeseen drug interaction. A balance of risks and benefits is essential and considered on an individual basis. Most relapsed patients with CLL suffer from secondary immunodeficiency and the administration of new agents has been associated with opportunistic infections. Patients require PJP prophylaxis throughout therapy and for at least 6 months afterwards ([Cheah and Fowler 2016](#_ENREF_16), [MHRA 2017](#_ENREF_78)) and should be managed as outlined under the supportive care section of this guideline.

**BTK-inhibitors (BTKi)**

Concomitant use of BTKi with drugs that strongly or moderately inhibit CYP3A4 (including Warfarin or other Vitamin K antagonists) should be avoided ([Janssen-Cilag 2017](#_ENREF_58)). Fish Oils and Vitamin E preparations should be avoided along with St John’s Wort. Grapefuit and Seville oranges must not be taken with BTKi.

Patients on BTKi may develop or have pre-existing conditions requiring anticoagulation or anti-platelet therapy. For patients already on Vitamin K antagonists who require BTKi therapy bleeding risk may be reduced by changing to a direct oral anticoagulant (DOAC) and considering dose reduction if risk benefit ratio allows. Alternative therapy such as PI3Ki may be considered. For patients on dual anti-platelet therapy, (e.g; following coronary artery stenting) withdrawal of one of these agents e.g. clopidogrel should be considered in consultation with the cardiologist ([Shatzel, Olson et al. 2017](#_ENREF_101)). Due to the occurrence of hypertension, atrial fibrillation and ventricular tachyarrhythmia in patients on ibrutinib, all patients should be closely monitored for cardiac symptoms ([MHRA 2017](#_ENREF_78)). Patients with a significant cardiac history should be considered for an alternative agent.

***PI3K* inhibitors (PI3Ki)**

PI3Ki can induce life-threatening colitis and pneumonitis. Patients with pre-existing gastrointestinal or pulmonary co-morbidities should therefore be considered for BTKi. In the advent of suspected colitis or pneumonitis, the PI3Ki should be stopped immediately, and topical and/or systemic immunosuppressive therapy initiated. Severe colitis can be managed with oral glucocorticoids ([Coutre, Barrientos et al. 2015](#_ENREF_20)). Patients on PI3Ki also require regular monitoring for hepatic dysfuction. Pneumocystis jirevicii pneumonia (PJP) and CMV reactivation have also been reported in patients treated with idelalisib. Consequently, it is advised that patients receiving idelalisib should also receive PJP prophylaxis and undergo regular monitoring for CMV reactivation.

**Venetoclax**

There is a significant risk of tumour lysis when initiating therapy with venetoclax ([Roberts, Davids et al. 2016](#_ENREF_92)) Dose-escalation over five weeks and strict Tumour Lysis Syndrome prophylaxis including admission of high-risk patients for dose escalation are indicated following local protocols.

**Autoimmune cytopenias (AIC)**

In the largest observational study of cytopenias in CLL, which included early stage patients, autoimmune cytopenias (AIC) occured in 5-10% of patients during their disease course and preceded the diagnosis of CLL in 9% of cases ([Dearden 2008](#_ENREF_22), [Zent, Ding et al. 2008](#_ENREF_115), [Hodgson, Ferrer et al. 2011](#_ENREF_54)). Many patients have no indications to treat the underlying CLL and can be managed with immunosuppression together with supportive measures as idiopathic AIC ([Go, Winters et al. 2017](#_ENREF_41)).

Up to 33% of CLL have a positive direct antiglobulin test (DAT) at some stage, but overt autoimmune haemolytic anaemia (AIHA) occurs less often. A positive DAT alone or past history of AIC is not a contra-indication to chemoimmunotherapy ([Borthakur, O'Brien et al. 2007](#_ENREF_8)). For patients with AIHA and CLL requiring treatment, most clinicians advocate immunosuppression before commencing CLL-directed therapy. There are no large controlled studies to guide chemoimmunotherapy choice in CLL patients with active AIHA and decisions are inferred from treatment emergent AIHA rates. Monotherapy with fludarabine and chlorambucil can precipitate AIHA and is best avoided in this setting. Caution is advised for re-challenging patients with a regime that previously caused severe AIC. RCD (rituximab, cyclophosphamide & dexamethasone), alemtuzumab or BCRi are effective alternatives ([Karlsson, Hansson et al. 2007](#_ENREF_63), [Kaufman, Limaye et al. 2009](#_ENREF_64)). A low incidence of treatment emergent AIHA has been reported for ibrutinib in the RESONATE front-line study and also a large series from Ohio ([Rogers, Ruppert et al. 2016](#_ENREF_93), [Montillo, O'Brien et al. 2017](#_ENREF_83)). Anecdotal case reports of concomitant AIHA & progressive CLL also show positive results with ibrutinib +/- steroids ([Molica and Polliack 2016](#_ENREF_82)).

Approximately 2-5 % CLL patients develop immune thrombocytopenia (ITP), mainly when not receiving CLL-directed treatment ([Visco, Ruggeri et al. 2008](#_ENREF_110)). About 30% of cases also have a history of AIHA (Evan’s syndrome). Response to first-line treatment with steroids or IV immunoglobulin is 50% to 60% ([Dearden 2008](#_ENREF_22)). Weekly rituximab for four weeks is an effective treatment. The TPO-receptor agonists, romiplostim and eltrombopag have shown response in CLL-associated ITP ([Norton and Roberts 2006](#_ENREF_87)). Splenectomy remains a treatment option for refractory cases and may achieve a long-term response in up to 70% of patients, although response is much lower in Evan’s Syndrome or chronic ITP.

Pure red cell aplasia and autoimmune neutropenia (AIN) are rare complications with incidence < 1%. Both are diagnoses of exclusion. The treatment approach is the same as for AIHA.

**Recommendation**

* **In patients with otherwise asymptomatic CLL that does not require therapy and concurrent auto-immune cytopenias, treatment should target the autoimmune complication (GRADE IV)**
* **Where auto-immune cytopenia is the dominant clinical feature, initial treatment should be with corticosteroids, intravenous immunoglobulin or rituximab (GRADE IV)**
* **For auto-immune cytopenias triggered by CLL directed therapy, the CLL treatment should be halted and immunosuppression commenced (GRADE IV)**

• **CLL directed therapy should be initiated if the dominant clinical feature is CLL, or if the auto-immune cytopenia fails to respond to immunosuppression. The choice of CLL therapy should be based on the considerations covered elsewhere in these guidelines (GRADE IV)**

The BSH Haemato-Oncology task force members at the time of writing this guideline were Dr Guy Pratt (chair), Dr Nilima Parry-Jones, Dr Alistair Whiteway, Dr Pamela McKay, Dr Simon Stern, Dr Jonathan Lambert, Dr Oliver Miles and Dr Elspeth Payne. The authors would like to thank them, and the BSH guidelines committee for their support in preparing this guideline.

**Declaration of Interests**

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All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

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**Review Process**

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website www.b-s-h.org.uk/guidelines/

**Disclaimer**

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

***Appendix 1***

*Idelalisib + rituximab inclusion criteria (*[*Furman, Sharman et al. 2014*](#_ENREF_36)*)*

1. CLL that had progressed within 24 months after their last treatment
2. Previous treatment must have included either a CD20 antibody–based regimen or at least two previous cytotoxic regimens.
3. Not able to receive cytotoxic agents for one or more of the following reasons:
4. severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies,
5. an estimated creatinine clearance of less than 60 ml per minute,
6. a score on the Cumulative Illness Rating Scale (CIRS) of more than 6 for coexisting illnesses not related to CLL.
7. 17p deletion or mutation (added by Cancer Drugs Fund)

*Ibrutinib trial inclusion criteria (*[*Byrd, Brown et al. 2014*](#_ENREF_12)*)*

1. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria:
	1. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog–based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles.
	2. Age ≥70 years, or age ≥65 and the presence of co-morbidities (CIRS≥6 or creatinine clearance <70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy regimen. CIRS score can be determined using a web-based tool.
	3. History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia.
	4. Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient has received at least one prior therapy.

Table 1: A summary of front-line RCTs in CLL patients

Table 2: A summary of relapsed/refractory RCTs in CLL patients

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