A Canadian Perspective on the Treatment of Unfit Patients with Chronic Lymphocytic Leukemia

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Medical Writer: Benjamin Fuerth, MSc, New Evidence

Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in the western world, accounting for approximately 11% of all hematological cancers.1 According to SEER (Surveillance Epidemiology and End Results) data from 2005 to 2009, the median age at diagnosis in the U.S. was approximately 72 years.2 In 2007, the overall age-standardized incidence rate for CLL in Canada was 5.0/100,000 people; 6.8/100,000 people for males and 3.6/100,000 people for females.3 The five-year relative survival ratios of CLL by sex in Canada, excluding Quebec, based on three years of cases from 2001 to 2003 was 76% (95% CI: 74%–78%) in men and 81% (95% CI: 78%–84%) in women.4

Purpose of this document

The majority of clinical trials in CLL to date have enrolled patients who were 10 to 15 years younger than the median age of patients diagnosed in the clinic.5,6 Furthermore, patients with CLL who meet the inclusion criteria for clinical trials tend to be physically fit and have fewer comorbidities, thus making the results unsuitable for patients who are unfit to receive more aggressive standard treatment options, such as FCR (fludarabine, cyclophosphamide, rituximab). As a result, clinicians lack the necessary evidence for determining which treatments work most effectively in this patient population.

This paper will discuss two major issues physicians encounter when treating unfit patients with CLL: (i) What factors enter into the decision that a patient is unfit for FCR therapy? (ii) What are the best treatment options for those patients who are deemed unfit? In addition to reviewing the current evidence, the regional practices of three Canadian experts from Nova Scotia, Quebec, and Alberta will be explored.

Assessing patient fitness

Formal and informal methods for assessing patient fitness for treatment are used. Formalized methods are often required to assess eligibility for clinical trials, whereas, in routine practice, many physicians assess fitness informally and apply a gestalt to individual patients.

The most commonly employed formal assessment is the Eastern Cooperative Oncology Group Performance Status (ECOG PS) because of its historical requirement in clinical trials and ease of use. The ECOG PS was designed to assess how a disease affects daily living based on criteria that classify the patient into one of five grades, from 0 to 5, where 0 indicates a level of physical function equivalent to predisease performance (Table 1).7 The results of this assessment are used to estimate a patient’s tolerance for aggressive treatment.8

The Cumulative Illness Rating Scale (CIRS) has recently emerged as a required assessment for clinical trial eligibility and many physicians are using it in routine practice to identify patients in the clinic who best resemble those who were enrolled in the FCR trials.8,9 The CIRS score assesses comorbidities as part of a patient’s fitness by assigning points to various conditions in different organ systems based on their severity.10 The number of points is then tabulated across all body systems with a low score indicating optimal health. See Appendix A for a detailed description of how to calculate the CIRS score.11

In addition to the CIRS score, a patient’s renal function, as measured by the creatinine clearance (CrCl) rate, is an important indicator of their ability to tolerate treatment. This is particularly important when considering a fludarabine-based regimen because of its excretion by the kidneys. For example, the German CLL Study Group assigned a CrCl rate of ≥70 mL/min combined with a CIRS score ≤6 as inclusion criteria in the pivotal phase III CLL8 study.9
A patient’s comorbidity level can also be assessed using the Charlson Comorbidity Index (Appendix B), which takes into account the number and severity of 19 predefined comorbid conditions. A weighted score is assigned to each condition based on its association with one-year mortality, as higher scores represent worse conditions. However, due to its cumbersome nature, it is not often used in the routine assessment of patients.

Determining which criteria are best suited for predicting treatment toxicity in older patients with varying levels of fitness is an ongoing field of research and new models, such as the Chemotherapy Risk Assessment Scale for High-Age Patients, are being tested. An in-depth discussion on this topic is beyond the scope of this paper but more information on this subject was published in a review by Balducci and Extermann in 2000.

### Categorizing patients into fitness types

Once a fitness score has been determined based on one or more of the systems discussed, it is possible to group patients into a fit, unfit, or frail group (Table 2).

### Expert discussion on definition of an unfit patient

In the context of CLL, an unfit patient is someone who cannot tolerate more aggressive treatments, such as FCR. As previously discussed, there are many ways to determine a patient’s level of fitness but there is no clear cut-off point. One way is by applying the exclusion criteria put forth by the German CLL Study Group in the CLL8 trial that categorized patients as unfit if they had one of the following scores: ECOG PS 2–4, a CIRS score >6, or a CrCl rate <70 mL/min. However, the disease can sometimes cause a high ECOG PS score and a milder pretreatment phase may improve a patient’s status to the point that one would consider increasing FCR to full dose. Another issue is that some clinicians find the CIRS system too sensitive such that it excludes many patients who might otherwise tolerate as well as benefit from treatment with FCR.

Without a proven objective tool for the assessment of patient fitness, clinicians often rely on experience to identify an unfit patient. Any patient with significant comorbidities or >65 years with comorbidity are examples of the kinds of patients that some clinicians might consider unfit for treatment with FCR. An example of a frail patient could be one who is 75 years with comorbidities, decreased PS, and unable to independently perform activities of daily living.

### Treatment goals

Establishing treatment goals for patients of all fitness levels with CLL is predicated upon striking a balance between efficacy and toxicity, while improving or at least maintaining the patient’s quality of life (QoL). Ideally, treatment will provide a complete response (CR) and long overall survival (OS) with minimal toxicities. If an OS benefit is not attainable, then a reasonable goal of therapy is to achieve a long progression-free survival (PFS). However, for some frail patients, less aggressive treatments may be required; for others, supportive or palliative treatment may be the best course. Taking the patient’s preference into consideration is important in any treatment decision.

### Expert discussion on factors that influence treatment goals

In addition to a patient’s physical function and comorbidities, there are other factors that are taken into consideration when assessing goals for therapy, such as the patient’s age, support network, willingness and ability to travel to receive care, and to some extent, risk status. These factors are not listed in order of importance and will likely interact to some degree.
The age of the patient will play a certain role. For instance, younger patients (≤65 years) without comorbidities may be eligible for transplant. For these younger patients, achieving a partial response (PR), a nodular complete response (nCR), or a CR is important to determine the timing of transplant. Older patients who are fit should be treated with the aim of improving PFS and OS. For frail patients, regardless of age, maintaining QoL by reducing symptoms or improving blood parameters should become the treatment goal.

Travelling distance from the treatment centre is an important factor in the decision to use oral agents because patients need to be able to come to the clinic at regular intervals to receive their intravenous (iv) chemotherapy and for monitoring of their toxicities and response. The younger and fitter a patient, the more likely the patient will feel able to travel, hence distance becomes more important when age and comorbidities are included. Also, many elderly patients do not drive themselves and are, therefore, reliant on public transit or family members to drive them to their healthcare appointments. Proximity to an acute care facility and to family or a support network is also important in predicting which patients might have difficulty managing the toxicities of more aggressive treatments. Ultimately, the willingness to travel to receive care is a patient decision. While distance may favour using oral agents for convenience, more aggressive chemotherapy or clinical trials may provide an added treatment-free interval which is more beneficial in the long run.

A patient’s risk status can have some influence in setting treatment goals. For instance, if a physician has an older patient who is slightly frail but could probably tolerate aggressive chemotherapy, the finding of 17p deletion may sway the physician to aim for palliation alone. A younger patient with the same chromosomal deletion would alternatively warrant aggressive therapy, aiming potentially for cure with transplant.

**FCR as a standard treatment for fit patients with CLL**

In recent years, fit patients with CLL have experienced a significant improvement in survival outcomes from the coadministration of chemotherapy and the immunotherapeutic agent rituximab, a monoclonal antibody directed against the B-cell membrane surface protein CD20.\(^{15}\) The successful addition of rituximab to fludarabine led to the development of other rituximab and chemotherapy combination regimens. For instance, phase II studies examining the addition of rituximab to FC (FCR) demonstrated high CR (≈70%) and overall response (OR) (≈95%) rates as initial therapy and efficacy in relapsed patients (CR = 30%, OR = 74%).\(^{16-18}\) These impressive results set the stage for the phase III CLL8 and REACH studies, which showed improved PFS after administration of FCR compared with FC in first-line patients with CLL (39.8 vs. 31.5 months; HR = 0.56 [95% CI: 0.43-0.71], \(p < 0.01\)) and in previously treated patients with CLL (26.7 vs. 21.7 months; HR = 0.76 [95% CI: 0.60-0.96], \(p = 0.02\)), respectively.\(^{9,15,19}\)

**FCR toxicities may prevent adherence in older, less fit patients with CLL**

Currently, there are insufficient data to support the use of FCR in older and less fit patients with CLL since initial trials for this regimen were conducted primarily in younger and fitter patients.\(^9\) However, some data suggest that the efficacy of FCR may be limited in older patients because of decreased treatment adherence due to the toxicities associated with fludarabine-based chemotherapy, such as cytopenias and major infections.\(^{18}\) Notably, there does not appear to be an age-related biological basis for a poor response to chemotherapy in patients with CLL.

Cells from 365 untreated patients with CLL, aged 31 to 87 years, were tested *ex vivo* for cytotoxic responses to a panel of drugs.\(^{20}\) The sensitivity of these cells to clinically used drugs, including

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**Table 2. Patient fitness types**

<table>
<thead>
<tr>
<th>Patient fitness</th>
<th>General Description</th>
<th>Index scores</th>
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</table>
| **Fit**         | Ideal candidate for FCR, ≤65 years with little to no comorbidity or >65 years with no comorbidity | Both of the following:  
  a) ECOG PS 0–2  
  b) CIRS ≤6 and CrCl ≥70 mL/min |
| **Unfit**       | Not a candidate for FCR, >65 years with comorbidity | One of the following:  
  a) ECOG PS 3–4  
  b) CIRS >6 or CrCl <70 mL/min |
| **Frail**       | Not a candidate for FCR, >65 years with multiple comorbidities, or >75 years with comorbidity | Both of the following:  
  a) ECOG PS 3–4  
  b) CIRS >6 and CrCl <70 mL/min |

*Note: The examples of patient fitness types in this table are only meant as general descriptions. Although the age of a patient is a consideration, it is not a sufficient indicator of the capacity to tolerate treatment.

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FCR = fludarabine, cyclophosphamide, rituximab
fludarabine, chlorambucil, and cyclophosphamide, had no correlation with the patient’s age.

In a study by Shvidel et al.21 of fludarabine-based chemotherapy for 32 elderly patients (median 70 years, range 65–87) and 50 younger patients (median 55 years, range 38–64) with CLL, the rates of toxicity, major infections, and hospitalizations were significantly higher for the elderly patients. As a result, the elderly patients had more courses of treatment delayed, fewer of them completed the treatment program (31.2% vs. 76%), and they had lower OR rates (59% vs. 82%).21

**Treatment options for unfit patients with CLL**

Examining the responses in subgroups of older and less fit patients from past clinical trials will help identify less aggressive treatment options that are effective for those who cannot tolerate FCR. See Appendix C for a detailed list of the dosing regimens and data from the studies reviewed in this paper.

Some of the most common antineoplastic agents used in clinical practice for treating CLL include chlorambucil, cyclophosphamide, and fludarabine. Both chlorambucil and cyclophosphamide are nitrogen mustards that act as alkylating agents, while fludarabine is a purine analogue. Bendamustine is a newer agent that has a unique chemical structure combining alkylating groups with a purine-like benzimidazole ring but its exact mechanism of action remains unknown.22

Chlorambucil has been used as a mainstay treatment for CLL for over 55 years because it has a convenient oral dosing and well-established adverse-event (AE) profile that make it a valuable option for frail patients or those who decline or are unsuitable for more intensive IV therapy.23

**Chlorambucil vs. fludarabine**

The CLL5 study by Eichhorst et al. was a phase III trial that examined first-line therapy with fludarabine (n = 93) or chlorambucil (n = 100) in older patients with CLL whose median ages in each arm were 71 and 70 years, respectively.24 Patients who were administered fludarabine, compared with chlorambucil, achieved greater OR rates (72% vs. 51%, \( p = 0.003 \)) and CR (7% vs. 0%, \( p = 0.011 \)).24 However, a significantly greater response did not translate into improved survival in this study.24

A Cochrane meta-analysis of four randomized trials comparing single agent purine analogues with alkylator-based regimens supported the findings of superior PFS with purine analogues (HR = 0.70 [95% CI: 0.61–0.82]).25 There was a trend towards improved OS with purine analogues in this study, but statistical significance was not reached. Recently, a long-term survival analysis from a previous study by Rai et al. (2000)26 showed evidence of a slight OS advantage for fludarabine versus chlorambucil.22 Despite improved efficacy, rates of neutropenia were higher with fludarabine than with chlorambucil.26

**Chlorambucil vs. fludarabine vs. fludarabine plus cyclophosphamide (FC)**

The much larger phase III UK CLL4 study randomly assigned 777 previously untreated patients with CLL to receive fludarabine plus cyclophosphamide (FC), chlorambucil, or fludarabine alone in a 1:2:1 ratio, respectively.24 For patients in each arm, the median age was 65 years. As was the case in the overall study population, FC elicited the best response rates compared with fludarabine or chlorambucil alone in the elderly patient subgroup (≥70 years), which comprised 30% of all patients in this trial.28 The median PFS for all patients was longer with FC (43 months) compared with chlorambucil (20 months) or fludarabine (23 months). Analyses of PFS for the elderly patients reached similar conclusions, showing that FC was more beneficial when comparing it with fludarabine or with chlorambucil.28 Remarkably, there were no significant differences in OS between treatment groups. Neutropenia and hospitalizations were more common with fludarabine and FC than chlorambucil.28 Nausea, vomiting, and alopecia were most frequent with FC.

**Fludarabine vs. FC**

The authors of the UK CLL4 trial performed a meta-analysis with additional results from two other trials that had compared FC and fludarabine. They concluded that FC provided better response rates and improved PFS compared with fludarabine.28-30 However, OS was not different between the two arms. Despite the improved efficacy of FC versus fludarabine, higher neutropenia rates were detected in the FC group (56% vs. 41%).28

**Low-dose FC**

Some phase II studies have investigated the efficacy and safety of low-dose FC in elderly patients. In 2000, Marotta et al. reported results from a study of low-dose FC involving 20 patients with progressive, advanced CLL refractory to conventional chemotherapy. The median age of these patients was 75 years.31 All patients were administered a median of three cycles of low-dose FC, on schedule. Low-dose FC yielded an OR rate of 85%. Three patients (15%) attained a CR; one of whom relapsed after 12 months, while the other two remained event free after 24 months. The toxicity profile showed four patients experienced grade 4 granulocytopenia and two patients had grade 3 anemia.

In a study by Forconi et al., 26 patients with CLL received an oral regimen of low-dose FC.32 The baseline characteristics of these patients were: median age 71 years, 85% had an ECOG PS ≥1, median CIRS score of 1 (range 1–3), and comorbidities were present in 80% of patients. Overall, patients in this study responded well to treatment with a 92% OR rate and a 46% CRu (complete response ‘unconfirmed’ by bone marrow biopsy) rate.32 At a median follow-up of 24 months, 92% of patients were alive and 62% of patients were still event free. Cycle
reductions due to hematological and nonhematological toxicities were needed for 34% of patients, while 8% of patients required hospitalization as a result of an AE. Despite the small sample sizes in both the Marotta and Forconi trials, lowering the dose of FC seems to be effective while producing lower rates of toxicity than standard dosing in elderly and comorbid patients with CLL.

Bendamustine

Bendamustine is another promising option for the treatment of CLL. A phase III study by Knauf et al.33,34 randomly assigned 319 treatment-naïve patients in a 1:1 ratio to receive bendamustine or chlorambucil for up to six cycles. In the bendamustine and chlorambucil arms, the patients’ respective median ages were 63 and 66 years and over 93% of patients had a PS of ≤1. At a median observation period of 54 months, bendamustine had improved the CR (21.0% vs. 10.8%) rate, and prolonged median PFS compared with chlorambucil (21.2 vs. 8.8 months, HR = 2.83, p<0.0001).34 In addition, significantly more patients who received chlorambucil progressed to further lines of treatment compared with those who received bendamustine (78.3% vs. 63.6%), (p = 0.004). Although OS was not different between the two arms, patients with an OR or a CR experienced a significantly longer OS than nonresponders or those without a CR.

A study by Niederle et al. of 92 patients with CLL receiving second-line treatment with bendamustine (n = 49) or fludarabine (n = 43) showed that bendamustine delivered better rates of OR (76% vs. 62%) and CR (27% vs. 9%).35 Median PFS was improved with bendamustine compared with fludarabine (20.1 vs. 14.8 months, HR = 0.87 [90% CI: 0.60–1.27]) and bendamustine also provided a longer OS (43.8 vs. 41.0 months, HR = 0.82).35

Lenalidomide

Lenalidomide is an immunomodulatory and antineoplastic drug that has shown clinical activity as a single oral agent for relapsed or refractory patients with CLL.36,37 In a phase II study of lenalidomide for previously untreated patients with CLL, the OR/PR rate was 56% for the 25 patients who had a median age of 60 years, but none reached a CR.38 At a median follow-up of 20.7 months, the estimated two-year PFS and OS for all patients was 89% and 92%, respectively. The most common toxicities of any grade were tumour flare, fatigue, neutropenia, and rash. Another phase II study of lenalidomide as initial therapy for CLL enrolled 60 patients who were older (median age 71 years), the majority of whom had a Charlson Comorbidity Index score of 1 or 2.39 These patients reached an OR rate of 65%, including a CR rate of 10%. At a median follow-up of 31 months, 88% of patients were alive and the estimated two-year PFS rate was 60%.

Addition of rituximab to chemotherapy backbones

Rituximab has only moderate activity as a single agent in CLL, probably related to the low levels of CD20 expression on B-cells.40 However, it has been shown to enhance efficacy when used in combination with chemotherapy. For example, an observational study analyzed SEER data for treatment-naïve patients diagnosed with CLL from 1999 to 2005 in order to compare OS for those who were infused with any type of chemotherapy plus rituximab (n = 292) or chemotherapy alone (n = 1,429).41 The median age for all patients at diagnosis was 77 years and 88% of patients in either group had a comorbidity index score ≤1. Patients who received rituximab plus chemotherapy had a longer median OS than those who received chemotherapy alone (52 vs. 34 months).41 The primary multivariate-adjusted comparisons of OS revealed that the addition of rituximab to chemotherapy was more beneficial for survival than chemotherapy alone in all patients (HR = 0.75). This was also the case in most of the patient subgroups, particularly for those with less advanced disease (HR = 0.57).

Fludarabine plus rituximab (FR)

Initial studies of rituximab combinations explored the addition of rituximab to fludarabine (FR). In the randomized CALGB 9712 phase II study by Byrd et al.42, 104 previously untreated patients with CLL were randomized to receive six monthly courses of fludarabine either concurrently or sequentially with rituximab, followed two months later by rituximab consolidation therapy. The median age of these patients was 64 years and at least 92% of patients had a PS of ≤1. The rates of response to treatment were slightly better for the concurrent arm compared with the sequential arm, as the OR rates were 90% vs. 77% and the CR rates were 47% vs. 28%42 After a long-term median follow-up of 117 months, the median PFS and OS for all patients were 42 months and 85 months, respectively.43 The results of a retrospective analysis by Byrd et al.44 showed significantly better PFS and OS in patients who received FR in the CALGB 9712 trial42, as compared with historical data from the CALGB 9011 trial26, in which a similar group of patients had received fludarabine monotherapy.

An observational study of SEER data revealed that fludarabine use, independent of other treatments, was associated with a 14% risk reduction in mortality.45 Furthermore, among patients in this study who received fludarabine-containing regimens (n = 737), the addition of rituximab to fludarabine-based therapy was associated with an even greater reduction in mortality compared with fludarabine alone (HR = 0.58 [95% CI: 0.40–0.84]).41

A retrospective analysis by Gerrie et al.46 reviewed the outcomes for 98 patients with CLL or small lymphocytic lymphoma (SLL) initially treated with FR. Patients in this study had a median age of 62 years, with 27% of patients aged ≥70 years, and 13% of patients had an ECOG PS of 2–3. The median time of treatment-free survival (TFS) was four years, with two-year and four-year TFS rates of 69% and 54%, respectively. The OS rates were 90% at two years and 73% at four years. Treatment with FR was tolerated equally well by all age groups as a median of six cycles of treatment was delivered and few patients required hospitalization (13%), or discontinued due to toxicities (13%).
A small clinical study by Guo et al. investigated FR as a treatment for 16 elderly patients with CLL who had a median age of 87 years and an average Charlson Comorbidity Score of 4.1. Patients responded favourably to treatment with high OR (81.3%) and CR (43.8%) rates. For survival outcomes at one, three, and five years of follow-up, the respective rates of PFS (100%, 62.5%, and 25%) and OS (100%, 68.8%, and 31.3%) were also quite favourable. Despite the lack of phase III studies, these results taken together suggest that adding rituximab to fludarabine improves PFS and OS.

**Dose-reduced fludarabine, cyclophosphamide, rituximab (FCR lite)**

The addition of rituximab to low-dose FC chemotherapy (FCR lite) has been investigated as a way to further improve the efficacy of treatment for unfit patients. A study by Smolej et al. assessed the efficacy and safety of FCR lite for 74 elderly and comorbid patients with CLL (n = 70) or SLL (n = 4). Half of these patients were receiving treatment in the first-line, while the remaining half was treated for relapsed or refractory disease. Patients had a median age of 70 years with a median CIRS score of 4. Responses to treatment were promising, as the OR and CR rates were 70% and 35%, respectively, but no data were available for PFS and OS. Toxicity was acceptable and manageable. The grade 3 or 4 AEs experienced by patients were neutropenia (51%), thrombocytopenia (13%), and anemia (10%). Serious infections occurred in 13% of patients and overall, three patients died after treatment failure.

Encouraging responses with FCR lite were also seen in a study of 63 evaluable patients with CLL who were all previously untreated. Enrolled patients had an ECOG Performance Status ≤2 and a median age of 58 years, nine of whom were ≥70 years old. Overall, 85% of patients completed all six cycles of treatment with dose reductions in 2% of cycles. The OR rate was 93%, as 73% of all patients reached a CR, including five of the nine patients ≥70 years. The median PFS was 5.8 years and the median OS had not yet been reached. Patients developed grade 3–4 neutropenia and infections in 11% and 6% of treatment cycles, respectively.

**Pentostatin, cyclophosphamide, rituximab (PCR)**

At standard dosing, pentostatin, cyclophosphamide, and rituximab (PCR) has been compared with FCR in a phase III trial involving younger patients with relatively good PS, proving to be comparably efficacious but also just as toxic. Shanafelt et al. recruited 64 previously untreated patients with CLL who had an ECOG PS of ≤3 and 28% of whom were aged ≥70 years for a study of PCR therapy. The responses to treatment were not significantly different between patients who had an ECOG PS of 0 and those with an ECOG PS of ≥1, as rates of OR (94% vs. 87%, p = 0.41) and CR (47% vs. 33%, p = 0.31) were high for both groups. Responses were also favourable regardless of the patient’s age. However, a poorer PS at baseline did correlate with more patients developing grade 3–4 neutropenia (60% vs. 24%, p = 0.005).

**Chlorambucil plus rituximab (Clb-R)**

A phase II study by Hillmen et al administered chlorambucil and rituximab (Clb-R) to 100 previously untreated patients with CLL whose median age was 70 years. The OR rate from an intent-to-treat analysis was 82%, which included 9%, 15%, and 58% of patients achieving a CR, a nodular PR, and a PR, respectively. The authors compared the responses in their study to historical data for patients on the chlorambucil arm in the UK CLL4 study and found that the addition of rituximab improved OR rates by 16% (95% CI: 6.0–26.0%). The median PFS for patients who received Clb-R was 23.5 months and the OS rate was 88%. Most of the AEs reported were grade 1–2. Overall, 37% of patients reported a total of 53 SAEs, the most common being febrile neutropenia (5 patients) and neutropenic sepsis (4 patients).

The ML21445 study was a two-step phase II trial of Clb-R that enrolled 97 previously untreated patients with CLL who were ineligible for FCR. As the second step, patients responding to therapy were subsequently randomized to receive either maintenance therapy with rituximab or clinical observation. The median age of patients was 70 years and 47.1% of patients had one or more comorbidities. Patients responded well to treatment achieving an OR rate of 81.2% and a CR rate of 16.5%. Furthermore, therapy was well tolerated as patients younger than 80 years were administered a median of six cycles of treatment and overall, the most common hematologic grade 3–4 toxicity was neutropenia occurring in 13.5% of patients.

**Bendamustine plus rituximab (BR)**

Following its success as a combination treatment in patients with relapsed or refractory CLL, bendamustine plus rituximab (BR) was subsequently used in combination for treatment of patients with CLL in the first-line setting. In a study by Fischer et al., 117 previously untreated patients with a median age of 64 years received BR. The rate of OR was 88.0% with 23.1% of patients achieving a CR. Following a median observation time of 27 months, the median event-free survival time was 33.9 months and 90.5% of patients were still alive. The AE profile showed patients most frequently experienced grade 3–4 thrombocytopenia (22.2%), neutropenia (19.7%), anemia (19.7%), and severe infections (7.7%).

The first interim results for 126 of 339 patients currently enrolled in the ongoing phase IIIb study known as MaBLe were recently reported at the American Society for Hematology 2012 Annual Meeting. This trial was designed to compare BR (n = 58) or Clb-R (n = 68) in a population of first-line and second-line patients with CLL who are closer in age (median, 74 years) and fitness to patients presenting in the clinic. After six cycles of treatment, patients in the BR arm had a superior CR rate compared with those in the Clb-R arm (24% vs. 10%; p = 0.033). At the end of treatment, the ORR was not significantly different between the BR and Clb-R arms (88% vs. 81%, respectively; p = 0.404). Safety data were similar between the two treatment arms, with the most common AE of any grade being neutropenia (BR: 42% vs. Clb-R: 46%).
**Lenalidomide plus rituximab**

Recently, favourable results were reported for a trial that studied the lenalidomide and rituximab combination regimen in 59 patients with relapsed or refractory CLL. Patients had a median age of 62 years and had received a median of two prior treatments, the most common being FCR. The OR rate was 66%, including a CR rate of 12%, and the median time to treatment failure was 17.4 months. At a median follow-up of 32.8 months for surviving patients, 17 deaths had occurred and the estimated three-year OS rate was 71%. The most frequent grade 3–4 hematologic toxicities occurring in these patients were neutropenia (73%), followed by thrombocytopenia (34%).

**Expert discussion on treatment options for unfit patients**

The following treatment options have been proposed for patients with CLL based on their fitness level (Table 3).

Considering the current standard of care, the first option to consider using for the treatment of borderline unfit patients would likely be dose-reduced FCR (FCR lite). For those patients with a lower level of fitness, the most commonly employed agents are fludarabine or chlorambucil, which may be used as single oral agents or combined with rituximab or prednisone. Other options occasionally considered include corticosteroids alone (e.g., high-dose methylprednisone or dexamethasone) or cyclophosphamide with or without rituximab or prednisone.

Bendamustine was approved for use in Canada in August 2012. It can be used alone or in combination with rituximab, ideally as first-line treatment in patients ineligible for fludarabine-containing regimens or at the time of relapse or progression. However, it remains to be determined how effective BR is compared with FCR; the results of the CLL10 trial are expected to report in the near future.

Patients who are refractory to fludarabine may benefit from cytogenetic testing in order to guide the next steps. If the patient has a 17p deletion but is otherwise fit, alemtuzumab may be beneficial. For patients who are unfit and are in a high-risk group, any combination can be tested, such as BR, rituximab plus lenalidomide, or rituximab and methylprednisone, with the aim of controlling disease, symptoms, and QoL.

Patients with renal dysfunction may benefit from dose-reduced fludarabine with added hydration, or bendamustine with or without rituximab, as bendamustine is not primarily excreted by the kidneys. Other potential options are chlorambucil and corticosteroids, as these agents can be used alone, in combination together, or each as its own regimen in combination with rituximab.

**Table 3. Proposed treatment options by patient fitness level**

<table>
<thead>
<tr>
<th>Patient fitness level</th>
<th>Treatment(s)</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit (i.e., ideal candidate for FCR)</td>
<td>FCR</td>
<td>OS (1st), PFS</td>
</tr>
<tr>
<td>Unfit (i.e., not a candidate for FCR, &gt;65 years with comorbidity)</td>
<td>FCR lite, FR, Clb-R, BR, PCR, Lenalidomide-R</td>
<td>PFS, CR, PR</td>
</tr>
<tr>
<td>Frail (i.e., not a candidate for FCR, &gt;65 years with multiple comorbidities or &gt;75 years with comorbidity)</td>
<td>Chlorambucil alone Fludarabine alone Lenalidomide alone</td>
<td>QoL</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; Clb-R = chlorambucil, rituximab; CR = complete response; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; OS = overall survival; PCR = pentostatin, cyclophosphamide, rituximab; PFS = progression-free survival; PR = partial response; QoL = quality of life; R = rituximab

**Conclusion**

Although accessibility will vary from province to province in Canada, there are evidently many options available to physicians for treating unfit patients with CLL. In reviewing data from recent studies, it is clear that regardless of the chemotherapy used for treatment, adding rituximab to any regimen provides additional benefit while having little impact on the overall toxicity profile.

At present, the best choice of therapy in order to balance efficacy and toxicity for patients who are unfit for treatment with FCR is probably either FCR lite or Bendamustine-R. However, the largest issue in CLL remains a lack of data to definitively support the superiority of any one treatment option over the other for these unfit patients. This will hopefully be corrected as investigators look to include a better representation of the average patient in future clinical trials. Already there are new treatments on the horizon, such as ibrutinib and obinutuzumab, which could change the therapeutic landscape in CLL.
## Appendix A: Calculating the 14-system modified Cumulative Illness Rating Scale (CIRS)*

<table>
<thead>
<tr>
<th>Systems</th>
<th>Description</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>- Any cardiac problem (angina, myocardial infarction, arrhythmia, valve problems)? - If affirmative, any medication taken for these problems? - Any heart surgery in the past?</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Vascular</td>
<td>- Any circulatory problem (includes peripheral atherosclerotic disease, aneurysm of the abdominal aorta...), hypertension, or cholesterol problem? - If affirmative, any medication taken for these problems? - Any vascular surgery in the past (bypass graft surgery of lower limbs, carotid endarterectomy...)?</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>- Any blood problem (anemia, leukemia, hypercoagulability or any other problem affecting the blood, the blood cells, the spleen, or the lymphatic system)? - If affirmative, any medication taken for these problems (such as iron)? Note: Patients taking anticoagulants belong to this system if the main problem is hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in Cardiac.</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>- Any respiratory problem (asthma, emphysema, bronchitis, pulmonary embolism)? - If affirmative, any medication taken for these problems (such as pressurized aerosols)? - Any lung surgery? - Cigarette smoking? How many packs per day? For how long? Pack years = number of packs per day x the number of years smoked (example: 1 pack per day for 20 years = 20 pack years) Smoker up to 20 pack years: Rated 1 Smoker from 21 to 40 pack years: Rated 2 Smoker over 40 pack years: Rated 3</td>
<td></td>
</tr>
<tr>
<td>Ophthalmological and otorhinolaryngology</td>
<td>- Any problem with eyes (glaucoma, cataract, important lost of vision), ears (includes important hearing impairment), nose, throat, voice? - Any medication taken for these problems (such as eye drops)? Note: Vertigo and dizziness are included in this section, unless they are of neurological origin.</td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>- Any problem with stomach or digestion (includes the esophagus, the stomach, and the duodenum)? - If affirmative, any medication taken for these problems? - Any surgery for the stomach or the esophagus?</td>
<td></td>
</tr>
<tr>
<td>Lower gastrointestinal</td>
<td>- Any intestinal problem (includes intestinal hernias, constipation, anal problems, incontinence...)? - If affirmative, any medication taken for these problems? - Any surgery for the abdomen?</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Patients taking anticoagulants belong to this system if the main problem is hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in Cardiac.
<table>
<thead>
<tr>
<th>Systems</th>
<th>Description</th>
<th>Scores</th>
</tr>
</thead>
</table>
| Hepatic and pancreatic        | - Any problem in the liver or the pancreas?  
- Any medication taken for these problems?  
- Any surgery for the liver or the pancreas?  
Note: Cholecystectomy is rated in this section.                                                                                     |        |
| Renal                         | - Any problem in the kidneys (impairment in function, infection...)?  
- If affirmative, any medication taken for these problems?  
- Any surgery for the kidneys?                                                                                                           |        |
| Genitourinary                 | - Any urinary problem (lithiasis, incontinence...)?  
- If affirmative, any medication taken for these problems?  
- Any surgery for the urinary bladder, for renal lithiasis?                                                                              |        |
| Musculoskeletal and tegumental| - Any problem in the skin, the joints, the bones, the muscles (includes arthrosis, osteoporosis, carpal tunnel, and any other skin or musculoskeletal problem)?  
- Any medication, anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor?                                                                 |        |
|                              | Note: Fibromyalgia is rated in this section, but it may also be rated in Psychiatric if necessary.                                                                                                            |        |
| Neurological                  | - Any neurological problem (cerebrovascular accident, peripheral neuropathy, headaches...)?  
- If affirmative, any medication taken for these problems?  
- Any surgery for these problems?                                                                                                           |        |
| Endocrine, metabolic, breast  | - Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem?  
- For obesity:  
  Body mass index (BMI) ≥30: Rated 1  
  BMI ≥30 + medication or moderate disability: Rated 2  
  BMI ≥45: Rated 3  
- Any medication? Surgery for any of these problems?  
- Any problem with breasts (dysplasia, cancer...)?  
- Surgery for these problems?  
- Menopause (or andropause in men)? Any hormone (the same for men in andropause)?  
- Menopause or andropause:  
  Without hormonotherapy or symptoms: Rated 0  
  Symptomatic or with hormonotherapy: Rated 1                                                                                             |        |
| Psychiatric                   | - Any problem of depression, anxiety, alcohol, drug abuse, or other problems?  
- Any medication taken for these problems?  
Note: Personality problems are rated in this section, but the patient’s chart should be checked.                                                                                          |        |
| Total score                   |                                                                                                                                                                                                            |        |


Appendix B: The Charlson Comorbidity Index*

<table>
<thead>
<tr>
<th>Assigned weights</th>
<th>Comorbid conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cerebrovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disease, dementia, diabetes, mild liver disease, myocardial infarct, peripheral vascular disease, ulcer disease</td>
</tr>
<tr>
<td>2</td>
<td>Any tumour, diabetes with end organ damage, hemiplegia, leukemia, lymphoma, moderate or severe renal disease</td>
</tr>
<tr>
<td>3</td>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td>6</td>
<td>AIDS, metastatic solid tumour</td>
</tr>
</tbody>
</table>

AIDS = acquired immunodeficiency syndrome  
A patient’s total score is equal to the sum of the assigned weights for each of the comorbidities listed in this table.  
## Appendix C: Clinical trial data of currently used treatments for CLL

<table>
<thead>
<tr>
<th>Ph</th>
<th>Tx Arms</th>
<th>Dose</th>
<th>Pts (N)</th>
<th>Median age, PS, &amp; prior Tx (N)</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>PFS (m)</th>
<th>PFS, HR (95% CI)</th>
<th>OS (m)</th>
<th>OS, HR (95% CI)</th>
<th>Safety/Other efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R + Chemo</td>
<td>(infused therapy only)</td>
<td>292</td>
<td>Age: 77</td>
<td>52</td>
<td>(41–62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo alone</td>
<td>(infused therapy only, i.e., oral meds w/o iv equivalent not in data)</td>
<td>1,429</td>
<td></td>
<td>Prior tx: 0</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Efficacy 40 m of f/u on average. Propensity score-adjusted OS comparisons (n = 2,040), relative to chemo alone: All pts: R + chemo: HR = 0.68 (0.57–0.82) R alone: HR = 0.80 (0.68–0.93)</td>
</tr>
<tr>
<td></td>
<td>R alone</td>
<td></td>
<td>319</td>
<td></td>
<td>53</td>
<td>(44-not defined)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>F: 25 mg/m² iv or 40 mg/m² po x 5 d x 6 cycles</td>
<td>194</td>
<td>Age: 64 (38–85)</td>
<td>80*</td>
<td>15*</td>
<td>38</td>
<td>nPR = 27</td>
<td>At 5 y: 10% (95% CI: 3%–16%)</td>
<td>At 5 y: 52% (95% CI: 42%–61%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>F: 25 mg/m² iv + C: 250 mg/m² x 3 d or F: 24 mg/m² po + C: 150 mg/m² x 5 d x 6 cycles</td>
<td>196</td>
<td>Age: 65 (40–86)</td>
<td>94*</td>
<td>38*</td>
<td>34</td>
<td>nPR = 23</td>
<td>At 5 y: 36% (95% CI: 28%–46%)</td>
<td>HR = 0.45 $p &lt; 0.00005$ vs. Clb and F</td>
<td>At 5 y: 54% (95% CI: 44%–64%)</td>
<td></td>
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</tr>
<tr>
<td>FC</td>
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</tr>
<tr>
<td>Clb</td>
<td>Clb: 10 mg/m² po x 7 d x 12 cycles</td>
<td>387</td>
<td>Age: 65 (35–85)</td>
<td>72</td>
<td>7</td>
<td>46</td>
<td>nPR = 19</td>
<td>At 5 y: 10% (95% CI: 6%–15%)</td>
<td>At 5 y: 59% (95% CI: 53%–66%)</td>
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<tr>
<td></td>
<td>F: 25 mg/m² iv x 5 d, q28d (up to 6 cycles)</td>
<td>93</td>
<td>Age: 71 ECOG ≤ 1: 98%</td>
<td>72*</td>
<td>7*</td>
<td>19</td>
<td></td>
<td>46</td>
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<tr>
<td></td>
<td>Clb: 0.4–0.8 mg/kg po x 14 d, q28d (up to 24 cycles)</td>
<td>100</td>
<td>Age: 70 ECOG ≤ 1: 91%</td>
<td>51</td>
<td>0</td>
<td>18</td>
<td></td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td>CTC gr 3–4 hematological AEs (F vs. Clb.) Leukocytopenia: 28% vs. 3% Neutropenia: 12% vs. 12% Anemia: 15% vs. 27% Thrombocytopenia: 15% vs. 20% Efficacy $p = 0.003$, OR for F vs. Clb $p = 0.011$, CR for F vs. Clb</td>
</tr>
</tbody>
</table>
## Appendix C: Clinical trial data of currently used treatments for CLL

<table>
<thead>
<tr>
<th>Ph</th>
<th>Tx Ams</th>
<th>Dose</th>
<th>Pts (N)</th>
<th>Median age, PS, &amp; prior Tx (N)</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>PFS (m)</th>
<th>PFS, HR (95% CI)</th>
<th>OS (m)</th>
<th>OS, HR (95% CI)</th>
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</tr>
<tr>
<td>III</td>
<td>FC</td>
<td>F: 25 mg/m² iv d1–3/cycle</td>
<td>409</td>
<td>Age: 61 (36–81), ≥65: 29% ECOG 0: 58%, CIRS 1 (0–8) untreated</td>
<td>OR: All = 80 ≥65 = 83</td>
<td>CR: All = 22 ≥65 = 24</td>
<td>At 3 y: All: 45%, ≥65: 43% Med: 32.8</td>
<td>All: HR = 0.56 (0.46–0.69), p &lt; 0.0001</td>
<td>All: HR = 0.67 (0.48–0.92), p = 0.012</td>
<td>Gr 3–4 neutropenia: FCR = 34%, FC = 21%, p &lt; 0.0001 Gr 3–4 leukocytopenia: FCR = 24%, FC = 12%, p &lt; 0.0001 Other AEs, including severe infections: p = NS Fatal AEs: FCR = 2%, FC = 3%</td>
<td></td>
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<tr>
<td></td>
<td>C: 250 mg/m² iv d1–3/cycle</td>
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<tr>
<td></td>
<td>+/-R: 375 mg/m² iv d0 of cycle 1; 500 mg/m² iv d1 of cycles 2–6 (28 d/cycle)</td>
<td>408</td>
<td>Age: 61 (30–80), ≥65: 31% ECOG 0: 56%, CIRS 1 (0–7) untreated</td>
<td>OR: All = 90 ≥65 = 93</td>
<td>CR: All = 44 ≥65 = 43</td>
<td>At 3 y: All: 65%, ≥65: 68% Med: 51.8</td>
<td>All: HR = 0.99 (0.58–1.69), p = 0.2871</td>
<td>All: HR = 0.83 (0.59–1.17), p &lt; 0.001</td>
<td>No major differences in AEs between tx arms Thrombocytopenia: 15% vs. 20% Efficacy *p = 0.003, OR for F vs. Clb †p = 0.011, CR for F vs. Clb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>2L post-FC</td>
<td>2L FCR</td>
<td>141</td>
<td>Post-FC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>TFS: 23</td>
<td>—</td>
<td>NR</td>
<td>—</td>
<td>Conclusion: Majority of CLL8 patients still in remission, hence 2L therapies captured here are mostly from earlier relapses. Results should be considered preliminary and descriptive trends due to the short follow-up time.</td>
</tr>
<tr>
<td></td>
<td>2L FC</td>
<td>2L FCR</td>
<td>91</td>
<td>Post-FC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>TFS: 8</td>
<td>—</td>
<td>NR</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2L B</td>
<td>2L BR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>TFS: 18</td>
<td>—</td>
<td>45</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2L BR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>TFS: 16</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>FC</td>
<td>F: 25 mg/m² iv d1–3/cycle</td>
<td>276</td>
<td>Age: 62 (35–81), &gt;70: 17% ECOG ≤1 Had previous tx</td>
<td>58.0</td>
<td>13.0</td>
<td>44.9</td>
<td>20.6</td>
<td>All: 0.65 (0.51–0.82), p &lt; 0.001</td>
<td>S2</td>
<td>0.83 (0.59–1.17), p = 0.2871</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: 250 mg/m² iv d1–3/cycle</td>
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<tr>
<td></td>
<td>+/-R: 375 mg/m² iv d1 of cycle 1; 500 mg/m² iv d1 of cycles 2–6 (28 d/cycle)</td>
<td>276</td>
<td>Age: 63 (35–83), &gt;70 = 17% ECOG ≤1 Had prior tx</td>
<td>69.9</td>
<td>24.3</td>
<td>45.7</td>
<td>30.6</td>
<td>&gt;70 (n = 93): 0.99 (0.58–1.69)</td>
<td>NR</td>
<td>—</td>
<td>—</td>
<td>No major differences in AEs between tx arms Thrombocytopenia: 15% vs. 20% Efficacy *p = 0.003, OR for F vs. Clb †p = 0.011, CR for F vs. Clb</td>
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<th>PFS, HR (95% CI)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FC vs. FCR for all: p = 0.001 ICI: p = 0.011, hCI: p = 0.01</td>
<td>All: 45 ICI: 44 hCI: 45</td>
<td>All: 45 ICI: 44 hCI: 45</td>
<td>FC vs. FCR for all: p = 0.099 ICI: p = 0.005 hCI: p = 0.02</td>
</tr>
<tr>
<td>FC</td>
<td>FC: Standard tx schedule</td>
<td>43</td>
<td>Age: 59 (43–78)</td>
<td>CIRS: 4 (hCI = CIRS &gt;6, ICI = CIRS &lt;6)</td>
<td>81</td>
<td>46</td>
<td>35</td>
<td>All: 19 ICI: 20 hCI: 20</td>
<td>FC vs. FCR for all: p = 0.001 ICI: p = 0.011, hCI: p = 0.01</td>
<td>All: 45 ICI: 44 hCI: 45</td>
<td>FC vs. FCR for all: p = 0.099 ICI: p = 0.005 hCI: p = 0.02</td>
<td></td>
</tr>
<tr>
<td>FCR</td>
<td>FCR: Standard tx schedule</td>
<td>47</td>
<td>No prior tx</td>
<td>94</td>
<td>70*</td>
<td>24</td>
<td>All: 43 ICI: 60 hCI: 40</td>
<td>FC vs. FCR for all: p = 0.001 ICI: p = 0.011, hCI: p = 0.01</td>
<td>All: 45 ICI: 44 hCI: 45</td>
<td>FC vs. FCR for all: p = 0.099 ICI: p = 0.005 hCI: p = 0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stadnik E, et al. ASH Annual Meeting Abstracts 2011;118:4616**

**FC**
- F: 25 mg/m²/d iv d2–4 of cycle 1 and d1–3 of cycles 2–6
- C: 250 mg/m²/day iv d2–4 of cycle 1 and d1–3 of cycles 2–6
- R: 375 mg/m² iv d1 of cycle 1 and 500 mg/m² iv d1 of cycles 2–6

Age: 60, >70 (n = 40)
- ECOG ≤3
- Prior tx = 2

- All: 74
- All: 30
- All: 30, nPR = 14
- All: 21
- >70: 13

- All: 46.5
- >70: 22

- (% of cycles):
  - Neutropenia: gr 3 = 22%, gr 4 = 3.4%
  - Thrombocytopenia: gr 3 = 12.5%, gr 4 = 7.0%
  - Anemia: gr 2 = 11.2%, gr 3–4 = 0.46% (CTC 2.0), gr 3 = 7.1%, gr 4 = 4.7% (CTC 3.0)
  - 16% of pts had ≥1 episode of pneumonia or sepsis


**FCR**
- F: 25 mg/m²/d iv d2–4 of cycle 1 and d1–3 of cycles 2–6
- C: 3.373 mg
- R: 3.212 mg

Age: 65.5 (45–77)
- All considered fit

- Mean dose per patient: F: 467 mg, C: 4.373 mg, R: 3.212 mg
- Mean dose per patient: F: 593 mg, C: 5.850 mg, R: 3.303 mg
- G-CSF: Med cumulative amt/pt = 135 x 10⁶ units


**FCR**
- Mean dose per patient: F: 467 mg, C: 4.373 mg, R: 3.212 mg

Age: 65.5 (45–77)
- All considered fit

- 16
- 75
- 44
- 31
- At 24 m: 35.4%
at 36 m: 13.3%

**FCR + G-CSF**
- Mean dose per patient: F: 593 mg, C: 5.850 mg, R: 3.303 mg

Age: 67 (52–78)
- All considered fit

- 16
- 94
- 56
- 38
- At 24 m: 100%at 36 m: 100%
### Appendix C: Clinical trial data of currently used treatments for CLL

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<thead>
<tr>
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<th>Tx Arms</th>
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<th>CR (%)</th>
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<th>PFS (m)</th>
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</tr>
<tr>
<td>Marotta G, et al. Hematologica 2000;85:1268–70</td>
<td>II, Low-dose FC</td>
<td>F: 15 mg/m² iv</td>
<td>20</td>
<td>Age: 75 Prior tx: 2+</td>
<td>85</td>
<td>15</td>
<td>70</td>
<td>TTP in PR: 10 m</td>
<td>Pts in CR have not relapsed</td>
<td>7 pts died (PR: 5, PD: 2)</td>
<td>—</td>
<td>Gr 4 granulocytopenia: 4 pts Gr 3 anemia: 2 pts</td>
</tr>
<tr>
<td>Smolej L, et al. ASH Annual Meeting Abstracts 2010;116:2466</td>
<td>FCR lite</td>
<td>F: 50% to 12 mg/m² iv or 20 mg/m² orally d1–3 C: 60% to 150 mg/m² iv/po d1-3 R: 100% to 375 mg/m² in 1st cycle, 500 mg/m² from 2nd cycle</td>
<td>70</td>
<td>Age: 70 CIRS: 4 (0–10)</td>
<td>70</td>
<td>35</td>
<td>NA</td>
<td>—</td>
<td>—</td>
<td>NA</td>
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<tr>
<td>Mulligan et al. ASH Annual Meeting Abstracts 2012;120:436</td>
<td>FRS</td>
<td>F: 24 mg/m² po d1–5 R: 375 mg/m² cycle 1, 500 mg/m² C2-6, iv d1</td>
<td>117/120</td>
<td>Age: 71.7 (65–83)</td>
<td>Post-cycle 3 (n = 85): CR = 3.2%, nPR = 3.5%, PR = 60%, SD = 3.5%, PD = 0%</td>
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<tr>
<td>FCR</td>
<td>F: 24 mg/m² po C: 150 mg/m² po d1–3 R: 375 mg/m² cycle 1, 500 mg/m² C2-6, iv d1</td>
<td>2m post-Rx (n = 66): CR = 3.4%, nPR = 13.6%, PR = 43.9%, SD = 7.6%, PD = 0%</td>
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<tr>
<td>FCRS</td>
<td>F: 24 mg/m² po C: 150 mg/m² po d1–5 R: 375 mg/m² cycle 1, 500 mg/m² C2-6, iv d1</td>
<td>2m post-Rx (n = 66): CR = 3.4%, nPR = 13.6%, PR = 43.9%, SD = 7.6%, PD = 0%</td>
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</tbody>
</table>

**Efficacy**

- Using stringent stopping criteria with delay of 2 weeks for recovery of grade 3–4 toxicity but no dose reduction, –40% of pts stop early due to toxicity, intercurrent illness or pt choice. Neither CIRS 0–6 nor age predicted for grade 3–4 toxicity.

**Safety**

- High OR rate of 92.3% at 2m post-Rx.
### Appendix C: Clinical trial data of currently used treatments for CLL

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<th>OR (%)</th>
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<th>PFS, HR (95% CI)</th>
<th>OS (m)</th>
<th>OS, HR (95% CI)</th>
<th>Safety/Other efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>FCR lite</td>
<td>6 cycles, q4w F: 20 mg/m² iv d2–4 C1, d1–3 C2–6 C: 150 mg/m²/iv d2-4 C1, d1–3 C2–6 R: 375 mg/m² iv on d1 C1, 500 mg/m² iv on d14 C1, d1 and d14 C2–6, used 500 mg/m² maintenance q3m</td>
<td>63/65</td>
<td>Age: 58 (36–85), ≥70: 9 pts</td>
<td>93</td>
<td>All: 73</td>
<td>All: 17 nPR: 3</td>
<td>Med: 5.8 yrs</td>
<td>1-yr: 93.2%, 3-yr: 84.6%, 5-yr: 66.9%</td>
<td>—</td>
<td>—</td>
<td>85% of pts completed all 6 courses with dose reduction in 2% of total cycles</td>
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<td>Gr. 3–4 AEs (% of cycles) Neutropenia: 11% Infections: 6%</td>
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<td>Gr 3–4 AEs Neutropenia: 76% Thrombocytopenia: 20% Anemia: 4% Infection: 20%</td>
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<td>Gr 3–4 AEs Neutropenia: 39% Thrombocytopenia: 10% Anemia: 0% Infection: 23%</td>
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<td>Tx discontinuation due to toxicity: 13% Tx-related deaths: 2%</td>
</tr>
</tbody>
</table>

| II  | FR concurrent | F: 25 mg/m² iv d1–5, q28d x 6 cycles R: 375 mg/m² d1, d4 of cycle 1, d1 of cycles 2–6 | 51      | Age: 63 (36–86), CALGB ≤1: 92% | 90      | 47     | 43     | At 2 y: 70% | From Woyach et al.: Med f/u of 117 m: PFS: 42, in both groups | After 23 m: 6 deaths | From Woyach et al.: Med f/u of 117 m: OS: 85, in both groups | Gr. 3–4 AEs Neutropenia: 76% Thrombocytopenia: 20% Anemia: 4% Infection: 20% |
|     | FR sequential | F: 25 mg/m² iv on d1–5, q28d x 6 cycles Pts w/ SD or better after 2 m received: R: 375 mg/m² iv x 4 weekly doses | 53      | Age: 63 (36–79), CALGB ≤1: 95% | 77      | 28     | 49     | At 2 y: 70% | PFS: 42, in both groups | After 23 m: 2 deaths | — | — | Gr. 3–4 AEs Neutropenia: 39% Thrombocytopenia: 10% Anemia: 0% Infection: 23% |
|     |         |                                                                     |         |                                |         |        |        |         |                  |         |                  | — | — | — |

| Gerrie AS, et al. Leuk Lymphoma 2012;53:77–82 | FR | F: 40 mg/m²/d orally or 25 mg/m² iv d1–5 R: 375 mg/m²/iv d1 q28d x 6 cycles | 98      | Age: 62 ≥70: 27% ECOG 2/3: 13% | —       | —      | —      | —       | — | — | — |
|     |         |                                                                     |         |                                |         |        |        |         |                  |         |                  | TFS: 2 y: All = 69%, 4 y: All = 54%, ≥70 = 68% Med for all pts = 4 y | OS: 2 y: All = 90%, 4 y: All = 73%, ≥70 = 52% | — | — | Tx discontinuation due to toxicity: 13% Tx-related deaths: 2% |

| Guo B, et al. Adv Ther 2012;29:178–86 | FR | F: 25 mg/m² iv d1, 3, 5 R: 375 mg/m²/iv d7 | 16      | Age: 87 Prior tx: 8 pts = 0, 8 pts = 1+ | 81.3    | 43.8   | 37.5   | PFS: 1 y = 100%, 3 y = 62.5%, y = 25% | OS: 1 y = 100%, 3 y = 68.8%, y = 31.3% | Gr 3–4 cytopenia: 2 pts Gr 3 infection: 1 pt No tx-related deaths | — | — | — | — |


### Appendix C: Clinical trial data of currently used treatments for CLL

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<th>Tx Arms</th>
<th>Dose</th>
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<th>Median age, PS, &amp; prior Tx (N)</th>
<th>OR (%)</th>
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<th>PR (%)</th>
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<th>OS (m)</th>
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</tr>
</tbody>
</table>
| II  | PCR     | P: 2 mg/m²  
C: 600 mg/m²  
R: 375 mg/m², 6 cycles | 64 | Age: ≥70: 28%  
ECOG ≤3: 0: 53%, 1: 38% | <70: 93  
≥70: 83 | <70: 41  
≥70: 39 |        |        |        |                  | Gr. 3–4 AEs (<70 vs. ≥70): Neutropenia: 35% vs. 56%  
Thrombocytopenia: 22% vs. 17%  
Anemia: 2% vs. 0% |
|     |         |      |         |                             |        |        |        |        |        |                  |                        |
| II  | FCR     | F: 20 mg/m² d1–5  
C: 600 mg/m² d1  
R: 375 mg/m² d1 (28-d cycles) | 92 | Age: 63.6  
ECOG ≤2: 0: 76.1%, 1: 22.8%  
Prior tx: 20.7% | All: 59.3  
>70: 43  
<70: 9 | All: 41.9  
>70: 9  
<70: 9 | Med: NR | Med: NR | 12-mos: 85.9%  
24-mos: 72.0% | Neutropenia gr 3–4: 69.3%  
Leukopenia gr 3–4: 34.1%  
Thrombocytopenia gr 3–4: 12.5%  
Pts with infections: 31%  
Tx-related deaths: 4 |
|     |         |      |         |                             |        |        |        |        |        |                  |                        |
| II  | BR      | B: 70 mg/m² on d1–2  
R: 375 mg/m² iv d 1  
1st cycle; 500 mg/m² iv for cycles 2-6 | 78 | Age: 66.5  
WHO ≤2 (93.6% WHO ≤1)  
Prior tx = 2 | All: 59  
>70: 73.1  
<70: 11.5 | All: 47.4  
>70: 61.5  
<70: 17 | All: 15.2 (12.5–17.9)  
All: 33.9 (25.5–42.1) | Med: NR | Med: NR | 12 m: 90.4%  
24 m: 86.7% | Neutropenia gr 3–4: 57.3%  
Leukopenia gr 3–4: 34.9%  
Thrombocytopenia gr 3–4: 15.9%  
Pts with infection: 36%  
Tx-related deaths: 4 |
|     |         |      |         |                             |        |        |        |        |        |                  |                        |
| II  | BR      | B: 90 mg/m² d1–2  
R: 375 mg/m² iv d0  
cycle 1; 500 mg/m² iv d1 of cycles 2–6 | 117 | Age: 64.6  
WHO ≤2 (95% WHO ≤1)  
Prior tx = 0 | All: 88.0  
>70: 84.6  
<70: 11.5 | All: 64.9  
>70: 73.1  
<70: 37.6 | All: 33.8  
>70: 37.6  
<70: 37.6 | Med: NR | Med: NR | 12 m: 90.5%  
24 m: 87.6% | Gr. 3–4 anemia: 16.6%  
Gr. 3–4 neutropenia: 23.1%  
Gr. 3–4 thrombocytopenia: 28.2%  
Severe infections: 12.8%  
Deaths: 4 pts on study tx |
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</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>BR</td>
<td>B: 90 mg/m² iv d1–2; R: 375 mg/m²² iv d0 of cycle 1; 500 mg/m² iv d1 of cycles 2–6</td>
<td>275</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>FCR</td>
<td>F: 25 mg/m² d1–3; C: 250 mg/m² iv d1–3; R: same as above</td>
<td>275</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>Casp</td>
<td>70.0</td>
<td>16.5</td>
<td>60</td>
<td>—</td>
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<td>Foa</td>
<td>70</td>
<td>81.2</td>
<td>2.4</td>
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<td>43–86</td>
<td>9</td>
<td>15</td>
<td>88 pts still alive</td>
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<tr>
<td>III</td>
<td>R-Clb</td>
<td>R: d1; 375 mg/m² iv cycle 1; 500 mg/m² cycles 2–6 Clb: d1–7; 10 mg/m²/d, q28d x 6 cycles</td>
<td>100</td>
<td>—</td>
<td>21.0</td>
<td>—</td>
<td>21.2</td>
<td>HR = 2.83, p &lt; 0.0001</td>
<td>No difference, except in pts with an OR or CR where B appears to prolong OS</td>
<td>31.7 vs. 10.1 m, p &lt; 0.0001</td>
<td>63.6% vs. 78.3%, p = 0.004</td>
<td>—</td>
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<tr>
<td></td>
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<td>B</td>
<td>—</td>
<td>Prior tx: 0</td>
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<td>—</td>
<td>8.8</td>
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<td></td>
<td></td>
<td>Clb</td>
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<td>—</td>
<td>10.8</td>
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<td>8.8</td>
<td>—</td>
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</table>

**CLL10 protocol of the German CLL-Study Group (GCLLSG)/ Eudract-2007-007587-21/ (NCT00769522)**


**OR and CR rates similar across the different Binet stages (OR rate: Binet A 86.4%, Binet B 79.6%, Binet C 78.6%) and age categories (OR rate: 60–64 y 84.6%, 65–69 y 85.2%, 70–74 y 75.0%, ≥75 y 81.0%). Two of four patients aged ≥80 y responded to induction tx.**

**Gr 3–4 neutropenia: 13.5%, 37% of pts reported 53 SAEs. The most common SAEs were febrile neutropenia (5 pts) and neutropenic sepsis (4 pts).**
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<th>OS (m)</th>
<th>OS, HR (95% CI)</th>
<th>Safety/Other efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>BR</td>
<td>B: 100 mg/m²/d d1–2 for up to 6 cycles</td>
<td>162</td>
<td>Age: 63.0, WHO ≤1: 96.3% Prior tx = 0</td>
<td>68</td>
<td>31</td>
<td>27</td>
<td>21.6</td>
<td><em>p &lt;0.0001</em></td>
<td>NR</td>
<td><em>p = 0.16</em></td>
<td>Gr 3–4 AEs: Neutropenia: 23.0% Thrombocytopenia: 11.8% Leukopenia: 14.3% Infection: 1.9%</td>
</tr>
<tr>
<td></td>
<td>Clb</td>
<td>Clb: 0.8 mg/kg on d &amp; 15 for up to 6 cycles</td>
<td>157</td>
<td>Age: 63.6, WHO ≤1: 93.2% Prior tx = 0</td>
<td>31</td>
<td>2</td>
<td>26</td>
<td>8.3</td>
<td>65.4</td>
<td>Gr 3–4 AEs: Neutropenia: 10.6% Thrombocytopenia: 7.9% Leukopenia: 1.3% Infection: 0.0%</td>
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</table>

| III | B | B: 100 mg/m² as 30-min infusion d1–2 of 4-w cycle (max 8 cycles) | 49 | Age: 67.5 | 76 | 27 | — | 20.1 | 0.87 (90% CI: 0.60–1.27) | 43.8 | 0.82 | Hematotoxicity slightly more frequent with B Gr 3–4 infections: 15% for both arms |

| IIIb | BR | B: 90 mg/m² (1L) or 70 mg/m² (2L) iv, d1–2 q4w cycles 1–6 | 58 | Age: 75 (49–87) | All: 88 | All: 24 | — | — | — | — | — | — | — |

| IIIb | Clb | Clb: 10 mg/m² po d1–7 q4w for up to 12 cycles | 68 | Age: 73 (44–91) | All: 81 | All: 10 | — | — | — | — | — | — | — |

| IIIb | R-Clb | R-Clb: 10 mg/m² po d1–7 q4w for up to 12 cycles | 68 | Age: 73 (44–91) | All: 81 | All: 10 | — | — | — | — | — | — | — |

---

1L = first line; 2L = second line; AEs = adverse events; amt = amount; B = bendamustine; BR = bendamustine, rituximab; C = cyclophosphamide; CALGB = Cancer and Leukemia Group B; Chemo = chemotherapy; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; CRu = complete response unconfirmed; CTC = common toxicity criteria; d = day; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; F = fludarabine; FC = fludarabine, cyclophosphamide; FCR = fludarabine, cyclophosphamide, rituximab; fu = follow-up; G-CSF = granulocyte colony-stimulating factor; gr = grade; HCl = high comorbidity index; HR = hazard ratio; iv = intravenous; ICl = low comorbidity index; m = month; med = median; NA = not available; NCI = National Cancer Institute; nPR = nodular partial response; NR = not reached; NS = not significant; OR = overall response; OS = overall survival; PD = progressive disease; PFS = progression-free survival; po = per os; PR = partial response; PS = performance status; Pts = patients; q28d = every 28 days; q3m = every 3 months; q4w = every four weeks; R = rituximab; R-CLL = relapsed chronic lymphocytic leukemia; SAEs = serious adverse events; SD = stable disease; SEER = Surveillance Epidemiology and End Results; TFS = treatment-free survival; TTP = time to progression;Tx = treatment; UT = untreated; UT-CLL = untreated chronic lymphocytic leukemia; WHO = World Health Organization; w = with; w/o = without; y = year
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chronic lymphocytic leukemia: a report from the International Workshop on Chronic
Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and
cyclophosphamide. Cancer treatts with chronic lymphocytic leukemia a randomised,


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Okken MM, Creech RH, Torney DC, et al. Toxicity and response criteria of the Eastern

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of
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Lamanna N. Tureter and chronic lymphocytic cancer cases, ICD-O-3 (October 2011 CCR file). (Accessed

Robak T, Mecitova M, Vriesendorp H, et al. Rituximab plus cyclophosphamide in elderly

Byrd JC, Blum R, Wierda W, et al. Addition of rituximab to fludarabine may prolong
progression-free survival and overall survival in patients with previously untreated chronic

Germis AS, Tosi CN, Ramadhan KM, et al. Oral fludarabine and rituximab as initial therapy
for chronic lymphocytic leukemia or small lymphocytic lymphoma: population-based ex-
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