Hematology Meeting Reports 2007; 1(5):25–32

Combination therapy with alemtuzumab: existing data and future studies

Robin Foà

Division of Hematology, University of 'La Sapienza', Rome, Italy

Corresponding author:
Robin Foà
Email: rfoa@bce.uniroma1.it

A B S T R A C T

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in the western world. CLL is generally considered an indolent disease affecting older patients greater than 60 years of age, but a significant proportion of patients diagnosed with CLL are less than 55 years old, or present with an aggressive and resistant form of CLL that is associated with serious infectious and autoimmune complications. Traditional first-line therapy for CLL utilises alkylating agents such as chlorambucil. In more recent years the antimetabolite fludarabine has been investigated in randomized clinical trials, producing notable results such as increased rates of overall response, complete response (CR) and progression-free survival. However, improved overall survival has not been observed in clinical trials. Patients who have achieved an apparent CR according to National Cancer Institute Working Group (NCI-WG) criteria might still have minimal residual disease (MRD). From these residual leukaemic cells, new disease can arise, leading to relapse and shortening of progression-free survival and overall survival. Recent development of highly sensitive techniques able to detect the presence of MRD at levels previously undetectable has meant that the potential for the complete eradication of MRD exists. In an attempt to capitalise on the promising results obtained with fludarabine, and to increase survival of patients with CLL, novel fludarabine combination therapies are now being used. Combinations of fludarabine with alkylating agents, anthracyclines and monoclonal antibodies have been shown to increase antitumour effects in clinical studies, both in previously untreated patients and in patients refractory to previous therapies, including fludarabine monotherapy. Specifically, combinations of fludarabine with the monoclonal antibody alemtuzumab have increased the complete and partial response rates in patients with CLL irrespective of their treatment history, and similar results have been obtained in other fludarabine-based antibody-chemotherapy combinations. These encouraging results have led to the design of several ongoing phase III trials of fludarabine combination therapy; the results of these studies will likely lead to improved strategies for individualised treatment of patients with CLL, prolonging overall survival and potentially leading to cure.

Introduction

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in the western world. The median age of patients presenting with CLL is 65–70 years, but a significant proportion of patients (20–30%) are aged <55 years at diagnosis. While CLL is generally considered an indolent disease, a significant number of patients present with an aggressive form of CLL that is characterized by rapid progression and resistance to standard therapy, and is frequently associated with serious infectious and autoimmune complications.[1,2] Although a large number of prognostic indicators for CLL have been established that could be used to optimise therapy, the only factor traditionally used to determine the timing of therapy is clinical staging, which does not determine an appropriate therapeutic approach to treatment of CLL.[1,2]

Rationale for combination therapy with alemtuzumab and fludarabine or fludarabine plus cyclophosphamide in chronic lymphocytic leukemia

Alkylating agents such as chlorambucil have been the traditional first-line therapy for CLL; more recently, therapies have involved the use of fludarabine as a single agent.[1,2] Use of fludarabine has increased overall response rates (ORR), complete response (CR) rates and progression-free survival (PFS), but not overall survival (OS). Although a high number of patients treated with these regimens meet the National Cancer Institute Working Group (NCI-WG) criteria for CR, this definition permits minimal residual disease (MRD) to persist, which greatly increases the risk of relapse.[3,4] MRD is defined using NCI-WG criteria as the presence of CLL cells in the peripheral blood or bone marrow. Detection of MRD requires assays that can measure very low levels of CLL cells; the two most common techniques used for detection of MRD are a highly sensitive flow cytometric assay[5] and polymerase chain reaction (PCR)-based techniques.[2]

Increasing survival is the goal of novel therapies

In an attempt to improve survival for CLL patients on fludarabine therapy, novel fludarabine-based combination therapies are now emerging. Combinations of fludarabine with a variety of agents, such as alkylating agents, anthracyclines and monoclonal antibodies, have shown increased antitumour effects, both in clinical studies and *in vitro*.[3,6–9] *In vitro* and *in vivo* data indicate that fludarabine combination therapies are successful due to complementary modes of action; the repair of DNA interstrand cross links induced by cyclophosphamide is inhibited by fludarabine and fludarabine can also down-regulate several complement-resistance proteins present on leukaemia cells, potentially leaving them vulnerable to complement-mediated cell lysis.19 Thus, synergistic effects are possible with combination treatment. Moreover, it has been suggested that monoclonal antibodies may sensitise malignant cells to chemotherapy.[11,20]

The monoclonal antibody alemtuzumab is directed against the CD52 cell surface antigen which is expressed on the surface of both normal and malignant B- and T-cell lymphocytes, monocytes and macrophages. The three cytotoxic mechanisms of action of alemtuzumab are complement-mediated cell lysis, antibody-dependent cellular cytotoxicity and induction of apoptosis.[21,22] Alemtuzumab is approved for the treatment of fludarabine-refractory CLL. A standard dosing regimen of 30 mg three times a week for up to 12 weeks resulted in an ORR

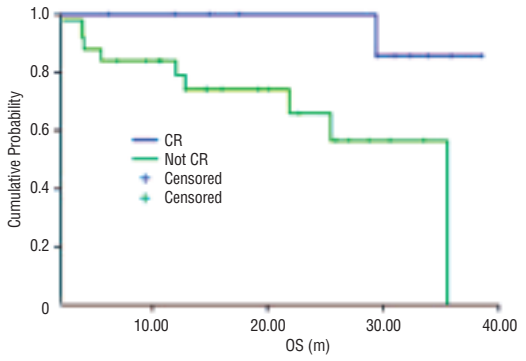

Figure 1: Overall survival (OS) in correlation to response. The median follow-up time was 15 months. Median OS time for patients who achieved complete response (CR) has not been reached.[33] Reproduced from Elter T, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukaemia: results of a phase II trial. *J Clin Oncol 2005;23:7024-31. Reprinted with permission from the American Society of Clinical Oncology.*

of 33% in fludarabine-refractory patients[23,24] and 83% in previously untreated patients.[25]

Alemtuzumab monotherapy is highly active in CLL, and is able to reduce the disease burden in both the blood and bone marrow of CLL patients to undetectable levels.[5,26,27] Eradication of MRD with alemtuzumab therapy is associated with prolonged survival[4,28,29] and patients without significant lymphadenopathy receiving alemtuzumab therapy have shown impressive response rates, although a lower response rate has been noted in patients with bulky lymph nodes.[24,30]

More recent studies of alemtuzumab monotherapy continue to illustrate its efficacy in both previously untreated patients and patients in relapse from or unresponsive to previous therapy. Twenty-one patients in complete or partial remission after fludarabine or fludarabine plus cyclophosphamide (FC) induction chemotherapy were randomised to receive either consolidation therapy consisting of alemtuzumab 30 mg 3 times weekly for up to 12 weeks or no further treatment.[31] Although the study was discontinued due to a high rate of severe infections, significant increases in long-term PFS were associated with alemtuzumab consolidation therapy compared with observation alone. Similarly, a response rate of 88.6% was seen in an interim analysis of a group of 38 patients either refractory (31.6%) to or in relapse (68.4%) after previous therapy (median number of prior therapies = 1; range 1–4).[32] CR was seen in 45.8% of these patients; 2.9% had an unconfirmed CR, and 42.8% had a partial response (PR). Toxicity in this study was manageable, with 10.6% of patients experiencing a grade 3–4 infection.

Efficacy of alemtuzumab plus chemotherapy combinations in patients with chronic lymphocytic leukemia

Several studies have shown increased efficacy of alemtuzumab plus various chemotherapy combinations in patients with CLL, even in those patients who were previously refractory to single-agent therapy. The combination of fludarabine and alemtuzumab (FluCam) induced a remission in 5 of 6 patients with progressive CLL characterized by significant bone marrow and lymph node involvement, and refractory to each agent when used as monotherapy.[15] A CR was seen in 1 patient in this study whose disease was eradicated from previously inaccessible nodal sites.[15] The responses observed in this study suggested that these agents in combination were acting synergistically, which provided a strong rationale for further studies.

Subsequent studies have indeed shown increased efficacy of antibody-chemotherapy combination treatments; a phase II study of the efficacy and safety of FluCam in 36 patients administered alemtuzumab 30 mg (after an initial dose escalation over 3 days) + fludarabine 30 mg/m^2 on 3 consecutive days every 28 days for up to 6 cycles had an ORR of 83% (11 CR, 19 PR, 1 stable disease [SD] and 5 progressive

Table 1: Response to combination therapy with FAND and alemtuzumab.

	2 FAND+ 2 FAND– Cam courses (Unmutated)		*2 FAND– Cam courses (Unmutated)*
	Relapsed 2 (1)	*Refractory 4 (2)*	*Refractory 7 (7)*
	6/6		6/7
ORRs	2	4	6
Molecular CR		2	-
Cytometric CR	1 (1)	1 (1)	1 (1)
CR	1		2 (2)
PR		1 (1)	3 (3)

diseases [PD]), and a median OS of 35.6 months (Figure 1).[33] The FluCam combination was deemed both effective and feasible in patients with relapsed and refractory CLL by the investigators (Elter et al. 2005).[33]

The combination of alemtuzumab with FAND (fludarabine, ARA-C, novantrone and dexamethasone) for the treatment of CLL has been evaluated.[34] Fludarabine 25 mg/m^2 iv (days 1, 2, 3), ARA-C 700 mg/m^2 iv (days 1, 2, 3), novantrone 10 mg/m^2 iv (day 1) and dexamethasone 20 mg iv (days 1, 2, 3) were administered in combination with alemtuzumab 30 mg iv (days 6, 7, 8). Clinical, cytometric and molecular responses were evaluated and the FAND-Cam combination proved effective in relapsed and refractory CLL patients (Table 1). Levels of haematological toxicity were considerable, particularly thrombocytopenia, although infections remained low and more than half of all patients did not experience cytomegalovirus (CMV) reactivation. This study is ongoing; while infections became more common with an increase in the number of patients evaluated, prophylactic treatment with valacyclovir reduced the rate of CMV reactivation from 67% to 11% and the FAND-Cam combination remained a feasible and effective treatment regimen, with a high rate of response (83–100%).[35]

The combined use of alemtuzumab and rituximab has also shown promising results in patients with relapsed and/or refractory CLL.[36,37] One trial of 48 patients with a range of lymphoid malignancies included 32 patients with relapsed or refractory CLL.[36] ORRs were 63% (20/32) in CLL patients and 52% (25/48) in the overall population after administration of rituximab 375 mg/m^2 weekly for 4 weeks plus alemtuzumab 30 mg (after initial dose escalation) twice weekly during weeks 2 and 4. Infection was reported in 52% of patients and 15% were symptomatic for CMV infection. A smaller trial evaluating this combination in another relapsed/refractory CLL population (n=12) had only 1 patient achieving a PR; however, the other 11 patients did show SD with a median of 101.5 days.[37] In addition, normalization of peripheral lymphocytosis occurred in all patients within a median of 23.5 days and no patient experienced CMV reactivation.

Ongoing trials with fludarabine

Several trials of fludarabine combination therapy are ongoing. In an interim analysis of 36 CLL patients previously refractory to fludarabine monotherapy participating in the UKCLL02 study, a large proportion of whom had risk factors for poor prognosis (unmutated IgV_H region, 17p deletion and/or 11q deletion, and p53 dysfunction), response rates after alemtuzumab monotherapy were: 2 MRD-negative CR, 1 MRD-positive CR, 11 PR (including 1 MRD-negative patient with cytopenia), 20 non-responders and 2 deaths.[38] Overall, 12 patients who failed to respond to alemtuzumab monotherapy received the FluCam combination, and 2 previous non-responders achieved a PR and 1 previous PR achieved a MRD-positive CR. The ORR for all patients was 44% and included 3 patients who were MRD-nega-

tive, suggesting that alemtuzumab was effective in high-risk patients with fludarabine-refractory CLL, with the FluCam combination potentially leading to improved response rates.[38] Additional ongoing studies of the FluCam combination in patients relapsed or refractory to previous treatment (in one case followed by alemtuzumab maintenance therapy[39]) have also shown that this treatment regimen is a safe and effective treatment for patients with CLL.[39-41]

Fludarabine/cyclophosphamide combination therapy has been shown to have greater efficacy than fludarabine alone.[42] Hence, several studies are investigating the combination of alemtuzumab added to fludarabine and cyclophosphamide (FC-Cam) in patients with relapsed CLL. In one ongoing phase II trial, the efficacy and safety of the FC-Cam regimen (oral fludarabine 40 mg/m^2/day plus oral cyclophosphamide 250 mg/m^2/day and subcutaneous alemtuzumab 10 mg on days 1–3, on a 28-day cycle for up to 6 cycles, after a short dose escalation from alemtuzumab 1 mg to 3 mg to 10 mg on consecutive days) was examined in an interim analysis of 3 patients that had completed treatment out of 9 patients enrolled to date.[43] The response rate in these patients was 100%; 1 CR and 2 PR, with 1 patient exhibiting blood MRD-negativity. The FC-Cam regimen was well tolerated as well as efficacious, providing a rationale for further investigation of the FC-Cam combination.[43] Indeed, the German CLL Study Group (GCLLSG) is also currently evaluating the efficacy of the FC-Cam combination in patients with relapsed or high-risk previously untreated CLL who have received one or two prior therapies (CLL2L study).

Salvage therapy, consisting of combined cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR), is also being studied in a phase II trial in heavily pre-treated patients with CLL.[44] Of the 66 patients enrolled to date, 44 were evaluated; two patients could not be evaluated for a response. Ten patients completed all 10 cycles, while 38 completed ≥3 cycles and there were two early deaths. Myelosuppression was the most frequent reason for treatment discontinuation. Grade 3 or 4 neutropenia was experienced by almost all patients and grade 3 or 4 thrombocytopenia was experienced by 57% of patients. CR, PR and OR rates in these patients were 27%, 38% and 65%, respectively. Higher OR rates were seen in fludarabine-sensitive patients and patients with earlier-stage disease. A higher CR rate was seen in fludarabine-sensitive patients. MRD disease was eliminated in 92% of patients achieving CR and 50% of patients achieving PR. Estimated median time to progression was ≥19 months for the overall population, and ≥20 and ≥10 months for patients achieving CR and PR, respectively. Estimated median survival times for the overall population, CR, PR and non-responders were 16, ≥27, 15 and 7 months, respectively. The analysis of these interim results has shown that CFAR is an active and well-tolerated regimen in heavily pre-treated patients with CLL.[44]

Further trials with fludarabine combination therapy: building on encouraging results

Based on the encouraging results of the phase II studies of fludarabine combination therapy, one phase III trail is ongoing and some others are in preparation. The promising results of the phase II study of FluCam combination therapy by Elter et al.[33] led to the initiation of an international, multicentre phase III study comparing fludarabine monotherapy with FluCam combination therapy in patients with CLL who are in relapse after one previous round of chemotherapy (CAM314 study). Treatment in the CAM314 study will consist of up to 6 cycles of either fludarabine 25 mg/m^2

over 5 days every 28 days or the FluCam combination (fludarabine and alemtuzumab at 30 mg/m^2 and 30 mg IV respectively) given for 3 consecutive days every 28 days.

The LLC0405 GIMEMA phase II pilot study is evaluating the use of different treatment strategies in patients ≤60 years of age with advanced stage and/or progressive CLL. Different regimens are selected based on a risk assessment performed using individual patients' biological profiles; high risk patients (e.g. those with 17p13 deletions or p53 mutations) will receive FluCam combination therapy plus stem cell transplantation or alemtuzumab consolidation in the presence of residual disease. Patients considered at standard risk will receive 4 cycles of fludarabine plus cyclophosphamide (FC), followed by alemtuzumab therapy for patients who do not achieve CR; patients with complete immunologic remission will receive an additional 2 cycles of chemotherapy, while patients achieving a molecular CR will undergo a stem cell collection.

Additional comparative phase III trials comparing FC-Cam with FCR in relapsed CLL or as a first-line regimen are currently planned through major European study groups and one trial is ongoing. The HOVON 68 study is an open-label, randomized, phase III study comparing FC with FC-Cam in previously untreated patients aged 18-75 years with biological high-risk CLL. Biological high-risk is defined as unmutated IgVH genes (≥98% homology with germ-line sequences) and/or deletions of 17p, deletions of 11q and/or trisomy 12. Patients enrolled in the HOVON 68 study will have symptomatic (defined according to NCI criteria) stage A or B, or stage C disease. Patients will undergo 6 cycles of therapy; those who have not achieved at least PR by the end of 3 cycles will be taken off the protocol. The primary endpoint is PFS.[45]

Conclusions

The modern approach to the management of CLL is still evolving, but the emphasis is clearly focused on the development of a biology-based diagnostic, prognostic and therapeutic algorithm, in an effort to tailor treatment strategies to an individual according to the biologic disease profile. Awareness of MRD and its effect on survival in patients with CLL has also led to earlier and more aggressive treatment with the aim of eradicating residual disease and prolonging survival. The potential for immunochemotherapy treatment combinations to achieve enhanced treatment response and increased life expectancy in patients with CLL will become clearer as further data become available.

References

1. Gentile M, Mauro FR, Guarini A, et al. New developments in the diagnosis, prognosis and treatment of chronic lymphocytic leukemia. Curr Opin Oncol 2005; 17:597–604.
2. Hillmen P. Beyond detectable minimal residual disease in chronic lymphocytic leukemia. Semin Oncol 2006;33 (2 suppl. 5):S23–8.
3. O'Brien SM, Kantarjian HM, Cortes J, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. J Clin Oncol 2001;19:1414–20.
4. Wendtner CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission. Experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004;18:1093–101.
5. Rawstron AC, Kennedy B, Evans P, et al. Quantification of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy. Blood 2001;98:29–35.
6. McLaughlin P, Hagemeister FB, Romaguera JE, et al. Fludarabine, mitoxantrone, and dexamethasone: An effective new regimen for indolent lymphoma. J Clin Oncol 1996;14:1262–8.
7. Bellosillo B, Villamor N, Colomer D, et al. In vitro evaluation of fludarabine in combination with cyclophos-

phamide and/or mitoxantrone in B–cell chronic lymphocytic leukemia. Blood 1999;94:2836–43.
8. Rummel MJ, Kafer G, Pfreundschuh M, et al. Fludarabine and epirubicin in the treatment of chronic lymphocytic leukaemia: A German multicenter phase II study. Ann Oncol 1999;10:183–8.
9. Flinn IW, Byrd JC, Morrison C, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. Blood 2000;96:71–5.
10. Kano Y, Akutsu M, Tsunoda S, et al. In vitro cytotoxic effects of fludarabine (2-F-ara-A) in combination with commonly used antileukemic agents by isobologram analysis. Leukemia 2000;14:379–88.
11. Keating MJ, O'Brien S, Lerner S, et al. Combination chemo-antibody therapy with fludarabine (F), cyclophosphamide (C) and rituximab (R) achieves a high CR rate in previously untreated chronic lymphocytic leukemia (CLL). Blood 2000 96:541a, Abstract 2214.
12. Di Gaetano N, Xiao Y, Erba E, et al. Synergism between fludarabine and rituximab revealed in a follicular lymphoma cell line resistant to the cytotoxic activity of either drug alone. Br J Haematol 2001;114:800–9.
13. Hallek M, Schmitt B, Wilhelm M, et al. Fludarabine plus cyclophosphamide is an efficient treatment for advanced chronic lymphocytic leukaemia (CLL): results of a phase II study of the German CLL Study Group. Br J Haematol 2001;114:342–8.
14. Wierda W, O'Brien S, Albitar M, et al. Combined fludarabine, cyclophosphamide, and rituximab achieves a high complete remission rate as initial treatment for chronic lymphocytic leukemia. Blood 2001;98:771a, Abstract 3210.
15. Kennedy B, Rawstron A, Carter C, et al. Campath-1H and fludarabine in combination are highly active in refractory chronic lymphocytic leukemia. Blood 2002; 99:2245–7.
16. Mauro FR, Foa R, Meloni G, et al. Fludarabine, ara-C, novantrone and dexamethasone (FAND) in previously treated chronic lymphocytic leukemia patients. Haematologica 2002;87:926–33.
17. Schulz H, Klein SK, Rehwald U, et al. Phase 2 study of a combined immunochemotherapy using rituximab and fludarabine in patients with chronic lymphocytic leukemia. Blood 2002;100:3115–20.
18. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23: 4079–88.
19. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070–8.
20. Demidem A, Hanna N, Hariharan H, et al. Chimeric antiCD20 antibody (IDEC-C2B8) is apoptotic and sensitizes drug resistant human B cell lymphomas and AIDS related lymphomas to the cytotoxic effect of CDDP, VP-16 and toxins [abstract]. FASEB J 1995; 9: 206a.
21. Bindon CI, Hale G, Waldmann H. Importance of antigen specificity for complement-mediated lysis by monoclonal antibodies. Eur J Immunol 1988;18:1507–14.
22. Xia MQ, Hale G, Waldmann H. Efficient complement-mediated lysis of cells containing the CAMPATH-1 (CDw52) antigen. Mol Immunol 1993;30:1089–96.
23. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554–61.
24. Rai KR, Freter CE, Mercier RJ, et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002;20:3891–7.
25. Hillmen P, Skotnicki A, Robak T, et al. Preliminary phase III efficacy and safety of alemtuzumab vs chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia (BCLL). J Clin Oncol 2006; 24(18 Suppl): Abstract No 6511.
26. Dyer MJ, Kelswy SM, Mackary HJ, et al. In vivo 'purging' of residual disease in CLL with Campath-1H. Br J Haematol 1997;97:669–72.
27. O'Brien SM, Thomas DA, Cortes J, et al. Campath-1H for minimal residual disease in CLL. Proc Am Soc Clin Oncol 2001;20:284a, Abstract 1132.
28. Rawstron AC, Kennedy B, Moreton P, et al. Early prediction of outcome and response to alemtuzumab therapy in chronic lymphocytic leukemia. Blood 2004;103: 2027–31.
29. Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol 2005;23:2971–9.
30. Kennedy B, Rawstron AC, Evans P, et al. Campath-1H therapy in 29 patients with refractory CLL: 'True' complete remission is an attainable goal. Blood 1999;94: 603a, Abstract 2683.
31. Schweighofer C, Ritgen M, Eichhorst B, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukemia (CLL) in first remission – long-term follow-up of a randomized phase III trials of the German CLL study group (GCLLSG). Blood 2006;108:33.
32. Bezares RF, Stemmelin G, Argentieri D, et al. Subcutaneous alemtuzumab in patients with refractory/relapsed B-cell CLL after a fludarabine-based regimen. An interim analysis. Blood 2006; 108:2843.
33. Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol 2005;23:7024–31.
34. Mauro FR, Gentile M, Giammartini E, et al. Fludarabine, Ara-C, Novantrone, and dexamethasone plus Campath-1H for the treatment of patients with chronic lymphocytic leukemia and adverse clinical and biologic prognostic features. Leuk Lymphoma 2005; 46(Suppl 1):P92.
35. Mauro FR, Giammartini E, De Propis MS, et al. Fludarabine, Ara-C, novantrone and dexamethasone plus campath-1H for the treatment of patients with chronic lymphocytic leukemia (CLL) and adverse clinical and

biologic prognostic features. Blood 2006; 108:2830.
36. Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003; 101:3413–5.
37. Nabhan C, Patton D, Gordon LI, et al. A pilot trial of rituximab and alemtuzumab combination therapy in patients with relapsed and/or refractory chronic lymphocytic leukemia (CLL). Leuk Lymphoma 2004;45:2269-73.
38. Sayala H, Moreton P, Jones RA, et al. Interim report of the UKCLL02 trial: A phase II study of subcutaneous alemtuzumab plus fludarabine in patients with fludarabine refractory CLL (on behalf of the NCRI CLL trials subgroup). Blood 2005;106:(Abstr 2120).
39. Kowal M, Dmoszynska A. Activity and safety of combined fludarabine and alemtuzumab followed by low-dose alemtuzumab maintenance therapy in patients with B-CLL. Blood 2006; 108:4993.
40. Egle A, Tinhofer I, Russ G, et al. Planned first safety and efficacy analysis of oral fludarabine combined with subcutaneous alemtuzumab in 2nd line therapy of B-chronic lymphocytic leukaemia (B-CLL): the FLUSALEM study. Blood 2006; 108:4990.
41. Brown JR, Stock W, Katzen HI, et al. Early estimates of safety for alemtuzumab combined with fludarabine for the treatment of relapsed/refractory B-cell chronic lymphocytic leukemia. Blood 2006; 108:4989.
42. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 2006;107:885–91.
43. Tedeschi A, Montillo M, Miqueleiz S, et al. Combination of fludarabine (FAMP) cyclophosphamide (CTX) and alemtuzumab for patients with relapsed chronic lymphocytic leukaemia (CLL). Blood 2005;106:abstract 5036.
44. Wierda W, O'Brien S, Ferrajoli A, et al. Salvage therapy with combined cyclophosphamide (C), fludarabine (F), alemtuzumab (A), and rituximab (R) (CFAR) for heavily pre-treated patients with CLL. Blood 2005;106: Abstract 719.
45. HOVON 68 study protocol. Available from: http://www.hovon.nl/