

A randomized phase III study in previously untreated patients with biological high-risk CLL: Fludarabine + cyclophosphamide (FC) versus FC + low-dose alemtuzumab

EudraCT nr.: 2005-000309-75

Page	Amendments with respect to protocol dated 14 March 2005	Date amendment
2	Amendment 1	20 October 2005
7	Amendment 2	14 April 2008

Changes: date 20 October 2005

Following the comments received from the CKTO and Danish Medicines Agency some changes have been made to the protocol. Furthermore, some changes have been introduced to strengthen patient safety. These and a few other changes and corrections are specified below. The new version of the protocol will be dated 20 October 2005.

Page numbers n1/n2 refer to the pages in the previous/new version of the protocol.

Page 6/6, Paragraph 4 Investigators and study administrative structure.

New text *Tomas Kozák* *University Hospital Kralovske Vinohrady, Prague*

Page 10/10, Paragraph 5.2.2 Alemtuzumab

New text *Hale et al. suggested that s.c. administration of alemtuzumab, especially in previously untreated patients, might lead to the formation of antibodies. To get a good incidence of this problem, sequential sera taken prior to alemtuzumab administration in each cycle will be stored and later tested for anti-alemtuzumab antibodies for all patients in the alemtuzumab arm.*

Page 13/13, Paragraph 8.1.2 Exclusion criteria

Old text Male and female patients of reproductive potential who are not practicing effective means of contraception

New text Male and female patients of reproductive potential who are not practicing effective means of contraception, *these include oral contraceptives, intrauterine device, depot injection of gestagen, subdermal implantation, hormonal vaginal ring and transdermal depot plaster. These methods must be applied for the entire protocol treatment period, and for patients treated with alemtuzumab until at least 6 months after the end of alemtuzumab administration.*

Page 15/15, Paragraph 9.6 Special management orders and concomitant medication

New text

- *Patients who receive alemtuzumab should be pretreated 1 hour before the alemtuzumab injection with paracetamol 1g p.o. and antihistaminic according to local routine. Corticosteroids are allowed in patients who experience severe cutaneous reaction, in doses according to local practice, but continuous use of corticosteroids should be avoided, in order to minimize immunosuppression. Following the first 3 alemtuzumab injections (cycle 1) and the alemtuzumab injection of cycle 2, the patient will stay in the out patient clinic for at least 4 hours for observation. If no severe adverse reactions have been observed following the alemtuzumab injection of cycle 2, the post-alemtuzumab observation time may be reduced to 1 hour in the remaining 4 cycles.*
- *All patients should receive allopurinol 300 mg daily day -2 until day 7 of cycle 1. During the following cycles allopurinol may be given according to local practice. In case of allopurinol allergy, alternative drugs (probenecid) may be used. During cycle 1 all patients will be instructed to secure relevant fluid intake, and will be monitored for tumor lysis syndrome with daily blood tests day 1-5 and day 8.*
- *In addition to the specifications in 9.3, G-CSF will be used for neutropenia throughout treatment according to the ASCO criteria (35).*

Page 16/17, Paragraph 11.2 Required investigations at entry, during treatment and during follow up

Old text

	At entry	Prior to each cycle	After cycle 3	End of protocol	Follow up (< 6 months after end of protocol)	Follow up (> 6 months after end of protocol)	At PD or PAPP
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Blood tests:							
Hematology	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X
Anti-viral antibodies	X						
CMV-PCR		X ¹	X ²	X	X ³		
EBV-PCR		X ³	o.i.	o.i.	o.i.		
Bone marrow biopsy	X		X ⁵	X		X ⁵	X
Molecular evaluations:							
PB Flow cytometry	X ⁴		X ^{4,5}	X ⁴		X ^{4,5}	X ⁴
BM Flow cytometry	X		X ⁵	X		X ⁵	X
PB FISH	X ^{4,6}						X ⁴
BM FISH	X ⁶						X
Mutational status	X ⁷						
MRD studies			X ⁵	X ⁵		X ⁵	X ⁵
PB storage future studies	X		X	X		X	X
BM storage future studies	X		X ⁵	X ⁵		X ⁵	X ⁵
Specific investigations:							
ECG	X						
CT scan ⁸	X		X	X		X	X
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.

- 1 weekly, alemtuzumab arm only
2 every 2nd week, alemtuzumab arm only
3 monthly for 3 months, alemtuzumab arm only
4 only if not done on bone marrow aspirate
5 only as confirmation of CR
6 may be done up to 3 months prior to inclusion
7 may be done at any time prior to inclusion
8 all tumor lesions at entry, follow target lesions accordingly
o.i. on indication

New text

	At entry	Prior to each cycle	After cycle 3	End of protocol	Follow up (< 6 months after end of protocol)	Follow up (> 6 months after end of protocol)	At PD or PAPER
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Blood tests:							
Hematology	X	X ¹	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X
Anti-viral antibodies	X						
CMV-PCR		X ²	X ³	X	X ⁴		
EBV-PCR		X ⁴	o.i.	o.i.	o.i.		
Bone marrow biopsy	X		X ⁵	X		X ⁶	X
Molecular evaluations:							
PB Flow cytometry	X		X ⁵	X ⁵		X ⁶	X
BM Flow cytometry	X ⁷		X ⁵	X ⁵		X ⁶	X ⁷
PB FISH	X ⁸						X
BM FISH	X ^{7,8}						X ⁷
Mutational status	X ⁹						
PB MRD studies			X ⁵	X ⁵		X ⁶	
BM MRD studies			X ⁵	X ⁵		X ⁶	
PB storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
BM storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
Specific investigations:							
ECG	X						
CT scan	X		X	X		X ⁶	X
Alemtuzumab antibodies ¹¹	X	X		X		X	
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.

¹ weekly, both treatment arms

² weekly, alemtuzumab arm only

³ every 2nd week, alemtuzumab arm only

⁴ monthly for 3 months, alemtuzumab arm only

⁵ only as confirmation of CR

⁶ at least once annually starting 6 months after end of protocol treatment

⁷ only if not done on PB

⁸ may be done up to 6 months prior to inclusion

⁹ may be done at any time prior to inclusion

¹⁰ any excess material

¹¹ alemtuzumab arm only

o.i. on indication

Page 18/19, Paragraph 11.2.7 Bone marrow biopsy

New text *At entry, after cycle 3 only as confirmation of CR, at the end of protocol treatment, at least annually during follow up starting 6 months after the end of protocol treatment and at progression.*

Page 18/19, Paragraph 11.2.8 Molecular evaluations

Deleted *Peripheral blood (and bone marrow aspirates at entry and if in CR) will be collected from all patients at study entry, after cycle 3 and after cycle 6. For patients achieving CR additional peripheral blood and bone marrow samples will be collected every sixth month until progression.*

Page 18/19, Paragraph 11.2.8 Molecular evaluations

New text *Flow cytometry*

At entry on PB (on BM if not done on PB), after cycle 3 on PB and BM only as confirmation of CR, at the end of protocol treatment on PB and BM only as confirmation of CR, at least annually on PB and BM during follow up starting 6 months after the end of protocol treatment and at progression on PB (on BM if not done on PB).

Page 18/19, Paragraph 11.2.8 Molecular evaluations

New text FISH
At entry on PB (on BM if not done on PB) and at progression on PB (on BM if not done on PB).

Page 18/20, Paragraph 11.2.8 Molecular evaluations

New text Mutational status and MRD studies
At entry mutational status on PB (on BM if not done on PB), after cycle 3 MRD studies on PB and BM only as confirmation of CR, at the end of protocol treatment MRD studies on PB and BM only as confirmation of CR and at least annual MRD studies on PB and BM during follow up starting 6 months after the end of protocol treatment.

Page 19/20, Paragraph 11.2.9 CT scan

Old text Imaging including CT of neck, thorax and abdomen. *All tumor lesions at entry, follow target lesions accordingly.*

New text *At entry, after cycle 3 only as confirmation of CR, at the end of protocol treatment and at least annually during follow up starting 6 months after the end of protocol treatment. Imaging including CT of neck, thorax, abdomen and pelvis at entry, after cycle 3, at the end of protocol treatment, at 6 months after end of protocol treatment and thereafter at least once annually.*

Page 19/20, Paragraph 11.2.10 Anti-alemtuzumab antibodies

New text **11.2.10 Anti-alemtuzumab antibodies**
Serum will be collected before alemtuzumab administration in all cycles and at 3 and 12 months after end of protocol treatment, to be frozen and stored at -70°C for later analysis. This is only applicable to patients treated in centers with the appropriate facilities for storage at -70°C.

Page 19/21, Paragraph 12.2 Alemtuzumab

New text *Furthermore, it has been demonstrated that s.c. alemtuzumab does not require dose escalation, but can be initiated as 30 mg injections (Lundin et al 2005).*

Page 20/21, Paragraph 13 Reporting serious adverse events

New text *In this study only grade ≥ 2 AE's will be reported.*

Page 21/23, Paragraph 13 Reporting serious adverse events

Old text At any time after the protocol treatment period, unexpected Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment *and ANY death (regardless the cause)* must also be reported to the HOVON Data Center using the same procedure, within 48 hours after the SAE or death was known to the investigator.

New text At any time after the protocol treatment period, unexpected Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, within 48 hours after the SAE or death was known to the investigator.

Page 26/28, Paragraph 17.4 Interim analysis

Old text Stopping or modification of the trial should be considered when five or more SAE's are reported with at least probable causal relationship with the treatment in one of the treatment arms.

New text Stopping or modification of the trial should be considered when *an excess of* five or more SAE's are reported with at least probable causal relationship with the treatment in one of the treatment arms *compared to the other treatment arm.*

Page 27/29, Paragraph 19 Trial insurance

Old text *Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary HOVON will extend the insurance to cover these patients.*

New text *The writing committee will ensure that risk insurance of patients from centers from outside the Netherlands is in place according to all applicable laws and regulations.*

Page 33/35, Paragraph 22 References

New text 28. Lundin J, Karlson C, Kimby E, Kennedy B, Strandberg M, Moreton P, Hillmen P, Osterborg A. Subcutaneous alemtuzumab without dose escalation in patients with previously treated B-cell chronic lymphocytic leukemia. *Leukemia and Lymphoma* 2005;46 (suppl 1):s92-93

Page 45/47, Appendix I Estimates of annual accrual per country

Old text

	Incidence	Age ≤ 75 years (~60 %)	High risk (~42 %)*	Symptomatic (~75 %)	Realistically
Denmark	250	150	63	47	9
Finland	150	90	37	28	6
The Netherlands	600	360	150	112	28
Norway	150	90	37	28	14
Poland	1100	660	275	206	15-25
Sweden	350	210	88	66	20-40
Total	2600	1560	650	487	92-122

New text

	Incidence	Age ≤ 75 years (~60 %)	High risk (~42 %)*	Symptomatic (~75 %)	Realistically
Czech Republic	unknown	unknown	unknown	unknown	6-10
Denmark	250	150	63	47	9
Finland	150	90	37	28	6
The Netherlands	600	360	150	112	28
Norway	150	90	37	28	14
Poland	1100	660	275	206	15-25
Sweden	350	210	88	66	20-40
Total	>2600	>1560	>650	>487	98-132

Changes: date 14 April 2008

4.1. Pathology review

Present text:

Once a patient is randomized, the local hematologist/pathologist as well as the central pathologist will be notified by e-mail. The local hematologist/pathologist will be asked to send 5 bone marrow biopsy slides (suitable to perform immunohistochemical stainings) as well as the immunophenotyping results to the review pathologist for his/her respective country. A copy of the results of the review will be sent to the local pathologist and to the HOVON Data Center. Confirmation of diagnosis is not necessary for randomization and start of treatment.

Amended text:

Once a patient is randomized, the local hematologist/pathologist will be asked to send a peripheral blood smear as well as the immunophenotyping results to the review pathologist for his/her respective country. A copy of the results of the review will be sent to the HOVON Data Center. Only in case of doubt will the bone marrow specimens be required for central review.

Reason for change: To bring diagnostic procedure in accordance with existing guidelines.

8.1.1. Inclusion criteria

Present text:

- Biological high-risk CLL*
- Patients with symptomatic** stage A, symptomatic** stage B or stage C (see appendix B)
- Age 18-75 years inclusive
- Written informed consent

* Biological high risk is defined as: ≥ 98 % homology of IgV_H genes with germ-line sequences and/or FISH with 17p deletions and/or 11q deletions and/or trisomy 12.

** Symptomatic CLL is defined according to the NCI criteria for active disease (Cheson et al. 1996, see appendix A).

Amended text:

- Biological high-risk CLL*
- Patients with symptomatic** stage A, symptomatic** stage B or stage C (see appendix B)
- Age 18-75 years inclusive
- Written informed consent

* Biological high risk is defined as: ≥ 98 % homology of IgV_H genes with germ-line sequences **and/or mutated CLL with usage of V_H3-21** and/or FISH with 17p deletions and/or 11q deletions and/or trisomy 12.

** Symptomatic CLL is defined according to the NCI criteria for active disease (Cheson et al. 1996, **Hallek et al. 2008**, see appendix A).

Reason for change: To bring definition of high risk CLL in accordance with current and new guidelines. Usage of V_H3-21 is associated with a poor prognosis in terms of overall and progression-free survival, which corresponds to that of unmutated CLL (1,2,4). V_H 3-21 usage is revealed by the the mutation status analysis and does not impose additional tests of the patients.

Change of patient information necessary: No.

8.1.2. Exclusion criteria

Present text (Exerpt):

- Known HIV positivity
- Active, uncontrolled infections

Amended text:

- Known seropositivity of HIV, **Hepatitis B and C**.
- Active, uncontrolled infections

Reason for change: To increase patient safety in accordance with current and new guidelines.

9.6. Special management orders and concomitant medication

Present text:

- All patients should receive pneumocystis carinii pneumonia (PCP) prophylaxis: sulphametoxazol with trimetoprim 400/80 mg daily or 800/160 mg three times a week throughout the study period until at least 3 months after the last treatment day. In case of intolerance to this drug, pentamidine inhalation 300 mg every month, dapsone 100 mg three times a week or any other documented PCP prevention is recommended (Fishman et al. 2001).
- All patients randomized to receive alemtuzumab should receive CMV prophylaxis: valaciclovir p.o. 1 g x 3. In patients with impaired renal function the dose should be reduced accordingly. This will also prevent HSV infection. For preemptive CMV treatment see appendix G.

Amended text:

- All patients should receive pneumocystis *Jiroveci* pneumonia (**PJP**) prophylaxis: sulphametoxazol with trimetoprim 400/80 mg daily or 800/160 mg three times a week throughout the study period **until at least 6 months after the last treatment day.**
- All patients randomized to receive alemtuzumab should receive herpes prophylaxis with either aciclovir 400 mg x 3-4 or valaciclovir 500 mg x 2.** For preemptive CMV treatment see appendix G.
 - When patients in the experimental arm develop fever, the possibility of a potentially severe opportunistic infection should be kept in mind. Physicians with special experience in opportunistic infections should be involved in the management of such patients, directly or by consultation.**

Reason for change: To bring protocol in agreement with new guidelines.³

Change of patient information necessary: No.

11. Required clinical evaluations

11.1 Time of clinical evaluations:

- After cycle 3: **Present text:** within 14 days after end of cycle 1.
Amended text: Prior to start of cycle 4.

Reason for change: To avoid that protocol treatment is terminated in responders with cytopenia.

- End of protocol: **Present text:** Within 14 days after cycle 6.
Amended text: At least 3 months after the last treatment, please see footnotes 12 and 13 to Table 11.2.

Reason for change: to allow cytopenia to resolve.

Table 11.2. **Present table text:**

11.2. Required investigations at entry, during treatment and during follow up

	At entry	Prior to each cycle	After cycle 3	End of protocol	Follow up (< 6 months after end of protocol)	Follow up (> 6 months after end of protocol)	At PD or PAPR
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Blood tests:							
Hematology	X	X ¹	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X
Anti-viral antibodies	X						
CMV-PCR		X ²	X ³	X	X ⁴		
EBV-PCR		X ⁴	o.i.	o.i.	o.i.		

Bone marrow biopsy	X		X ⁵	X		X ⁶	X
Molecular evaluations:							
PB Flow cytometry	X		X ⁵	X ⁵		X ⁶	X
BM Flow cytometry	X ⁷		X ⁵	X ⁵		X ⁶	X ⁷
PB FISH	X ⁸						X
BM FISH	X ^{7,8}						X ⁷
Mutational status	X ⁹						
PB MRD studies			X ⁵	X ⁵		X ⁶	
BM MRD studies			X ⁵	X ⁵		X ⁶	
PB storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
BM storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
Specific investigations:							
ECG	X						
CT scan	X		X	X		X ⁶	X
Alemtuzumab antibodies ¹¹	X	X		X		X	
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.

- 1 weekly, both treatment arms
2 weekly, alemtuzumab arm only
3 every 2nd week, alemtuzumab arm only
4 monthly for 3 months, alemtuzumab arm only
5 only as confirmation of CR
6 at least once annually starting 6 months after end of protocol treatment
7 only if not done on PB
8 may be done up to 6 months prior to inclusion
9 may be done at any time prior to inclusion
10 any excess material
11 alemtuzumab arm only
o.i. on indication

Table 11.2. Amended Table Text:

Required investigations at entry, during treatment and during follow up

	At entry	Prior to each cycle	After cycle 3	End of protocol	Follow up (< 6 months after end of protocol)	Follow up (> 6 months after end of protocol)	At PD or PAPER
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Blood tests:							
Hematology	X	X ¹	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X
Anti-viral antibodies	X						
CMV-PCR		X ²	X ³	X	X ⁴		
EBV-PCR		X ⁴	o.i.	o.i.	o.i.		
Bone marrow biopsy	X		X ⁵	X ¹²		X ⁶	X

Molecular evaluations:							
PB Flow cytometry	X		X ⁵	X ¹²		X ⁶	X
BM Flow cytometry	X ⁷		X ⁵	X ¹²		X ⁶	X ⁷
PB FISH	X ⁸						X
BM FISH	X ^{7,8}						X ⁷
Mutational status	X ⁹						
PB MRD studies			X ⁵	X ¹²		X ⁶	
BM MRD studies			X ⁵	X ¹²		X ⁶	
PB storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
BM storage future studies	X		X ¹⁰	X ¹⁰		X ^{6,10}	X
Specific investigations:							
ECG	X						
CT scan	X		X	X ¹³		X ⁶	X
Alemtuzumab antibodies ¹¹	X	X		X		X	
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.

¹ weekly, both treatment arms

² weekly, alemtuzumab arm only

³ every 2nd week, alemtuzumab arm only

⁴ **monthly for 6 months, alemtuzumab arm only**

⁵ only as confirmation of CR

⁶ at least once annually starting 6 months after end of protocol treatment

⁷ only if not done on PB

⁸ may be done up to 6 months prior to inclusion

⁹ may be done at any time prior to inclusion

¹⁰ any excess material

¹¹ alemtuzumab arm only

¹² **at least 3 months after the last treatment, and only if clinical, laboratory and CT results are compatible with CR**

¹³ **at least 3 months after the last treatment.**

o.i. on indication.

Table 11.2, footnotes:

Table 11.2.: Footnote⁴

Present text: ⁴ Monthly for 3 months, alemtuzumab arm only.

Amended text: ⁴ **Monthly for 6 months, alemtuzumab arm only**

Added footnote 12: **at least 3 months after the last treatment, and only if clinical, laboratory and CT results are compatible with CR**

Added footnote 13: **at least 3 months after the last treatment**

Reason for change: To bring protocol in accordance with existing guidelines.

Change of patient information necessary: No.

11.2.7 Bone marrow biopsy

Present text:

At entry, after cycle 3 only as confirmation of CR, at the end of protocol treatment, at least annually during follow up starting 6 months after the end of protocol treatment and at progression. For pathology study of

infiltration pattern and immunocytochemistry (required markers: CD5, CD19, CD20, CD23, CD79b, kappa, lambda, cyclin D1).

Amended text:

At entry, after cycle 3, at the end of protocol treatment only as confirmation of CR. In CR patients at least annually during follow up starting 6 months after the end of protocol treatment and at progression. For pathology study of immunocytochemistry of persisting nodules (required markers: CD5, CD19, CD20, CD23, CD79b, kappa, lambda, cyclin D1).

11.2.9 CT scan

Present text:

At entry, after cycle 3 only as confirmation of CR, at the end of protocol treatment and at least annually during follow up starting 6 months after the end of protocol treatment. Imaging including CT of neck, thorax, abdomen and pelvis at entry, after cycle 3, at the end of protocol treatment, at 6 months after end of protocol treatment and thereafter at least once annually.

Amended text:

At entry, after cycle 3, at the end of protocol treatment and at least annually during follow up starting 6 months after the end of protocol treatment, including CT of neck, thorax, abdomen and pelvis.

Appendix C Response criteria for CLL (NCI criteria with adjustments).

Complete response (CR):

Present text:

CR requires all of the following for at least 2 months:

- absence of lymphadenopathy;
- absence of hepatomegaly;
- absence of splenomegaly;
- absence of constitutional symptoms (see appendix A criteria 1a, 1b, 1c and 1d);
- normal blood counts defined as:
 - polymorphonuclear leukocyte count $\geq 1.5 \times 10^9/l$;
 - platelet count $> 100 \times 10^9/l$;
 - untransfused hemoglobin $> 6.8 \text{ mmol/l}$ ($> 11 \text{ g/dl}$);
- bone marrow $< 30 \%$ lymphocytes.

Amended text:

CR requires all of the following for at least 3 months:

- **Absence of clonal cells in peripheral blood**
- absence of lymphadenopathy;
- absence of hepatomegaly;

- absence of splenomegaly;
- absence of constitutional symptoms (see appendix A criteria 1a, 1b, 1c and 1d);
- normal blood counts defined as:
 - polymorphonuclear leukocyte count $\geq 1.5 \times 10^9/l$;
 - platelet count $> 100 \times 10^9/l$;
 - untransfused hemoglobin $> 6.8 \text{ mmol/l}$ ($> 11 \text{ g/dl}$);
- bone marrow without CLL cells by flow cytometry or immunochemistry.

CR with incomplete bone marrow recovery (CRi)

Patients who fulfill all the criteria for CR but who have persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL, but to drug toxicity.

Partial response (PR)**Present text:**

PR requires all of the following for at least 2 months:

- $\geq 50\%$ decrease in peripheral blood lymphocyte count;
- one or more of the following criteria:
 - $\geq 50\%$ reduction of lymphadenopathy;
 - $\geq 50\%$ reduction in size of liver (if abnormal prior to therapy);
 - $\geq 50\%$ reduction in size of spleen (if abnormal prior to therapy);
- one or more of the following criteria:
 - polymorphonuclear leucocyte count $\geq 1.5 \times 10^9/l$ (or 50 % increase compared to baseline);
 - platelet count $> 100 \times 10^9/l$ (or 50 % increase compared to baseline);
 - untransfused hemoglobin $> 11 \text{ g/dl}$ ($> 6.8 \text{ mmol/l}$) (or 50 % increase compared to baseline).

Amended text:

PR requires all of the following for at least 2 months:

- $\geq 50\%$ decrease in peripheral blood lymphocyte count;
- $\geq 50\%$ reduction of lymphadenopathy;
- $\geq 50\%$ reduction in size of liver (if abnormal prior to therapy);
- $\geq 50\%$ reduction in size of spleen (if abnormal prior to therapy);

The blood count should show one or more of the following results*:

- polymorphonuclear leucocyte count $\geq 1.5 \times 10^9/l$ (or 50 % increase compared to baseline);
- platelet count $> 100 \times 10^9/l$ (or 50 % increase compared to baseline);
- untransfused hemoglobin $> 11 \text{ g/dl}$ ($> 6.8 \text{ mmol/l}$) (or 50 % increase compared to baseline).

Bone Marrow: Patients otherwise in CR, but with B-lymphoid bone marrow nodules are designated PR.

***) Following cycle 3, response score based on clinical parameters only is allowed.**

Nodular PR: This section is deleted, due to the revised PR criteria (above).

Change of protocol: Yes

Change in patient information: No

Reason for change: To adjust according to new guidelines and to avoid termination of treatment protocol in responding but cytopenic patients after cycle III.

Appendix G Guidelines for CMV monitoring an treatment.

Duration of valganciclovir treatment

Present text: Full dose at least 10 days or until CMV PCR negativity and thereafter 900 mg x 1 as prophylaxis.

Amended text: Symptomatic: Duration of valganciclovir treatment 14-21 days until resolution of symptoms and negative test result or until 2 negative test results. Protocol treatment is held the same period. Asymptomatic: 7-14 days or until 2 consecutive negative test results. Protocol treatment not held.

Change of protocol: Yes

Change in patient information: No

Reason for change: Reduction of requested duration of valganciclovir treatment, according to new guidelines To bring protocol in accordance with present guidelines.³

22 References

References added:

- 1. Thorselius M, Kröber A, Murray F et al. Strikingly homologous immunoglobulin gene rearrangements and poor outcome in VH3-21-using chronic lymphocytic leukemia patients independent of geographic origin and mutational status. *Blood* 2006;107:2889-94.**
- 2. Kröber A, Bloehdorn J, Hafner S et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and V3-21 usage characterize discordance of ZAP-70 and VH mutation status in chronic lymphocytic leukemia. *J Clin Oncol.* 2006 Feb 20;24(6):969-75.**
- 3. O'Brien SM, Keating MJ, Mocarski ES Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clin Lymphoma Myeloma.* 2006 Sep;7(2):125-30.**
- 4. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. *Blood* 2008 Epub ahead of print.**