Rituximab maintenance for a maximum of 5 years after single agent rituximab induction in follicular lymphoma: Results of the randomized controlled phase 3 trial SAKK 35/03

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SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

Protocol SAKK 35/03
Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial

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1 TRIAL OVERVIEW

Protocol SAKK 35/03
Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial

OBJECTIVES
The primary objective of this trial is to investigate if maintenance with rituximab for 5 years or until relapse/progression, unacceptable toxicity or death is superior to 4 times maintenance with rituximab.

ENDPOINTS

Primary endpoint

- event-free survival

Secondary endpoints

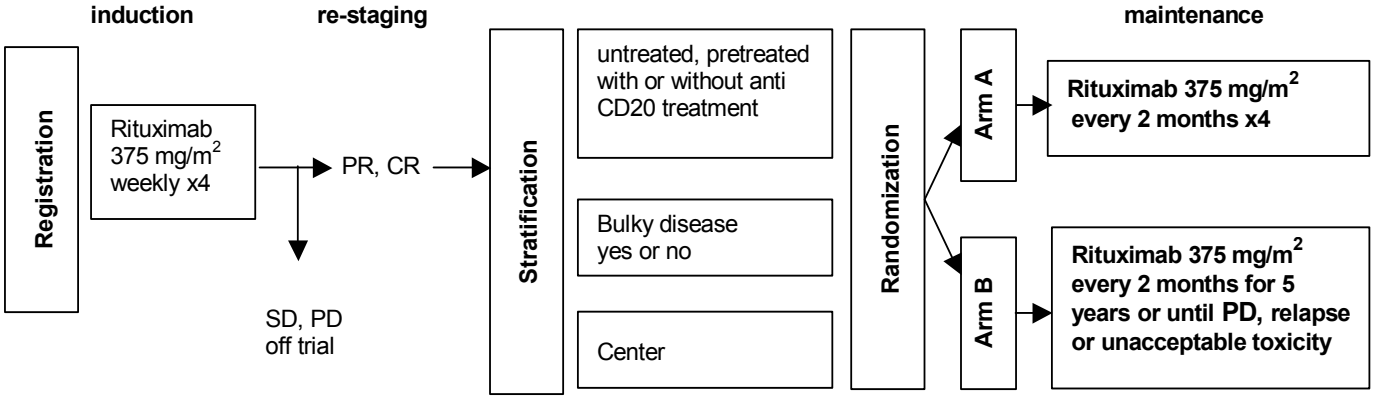
- progression-free survival
- overall survival
- objective response
- adverse reactions during and after maintenance treatment
- prognostic value of of baseline CRP
- molecular remission (for Swiss centers only)
- duration of molecular remission (for Swiss centers only)
- evolution of immunologic competence (for Swiss centers only)

Pharmaeconomical analysis

The totality of substantial direct costs to society incurred in the treatment.

TRIAL DESIGN

Prospective randomized phase III trial of 4 times maintenance versus 5 years maintenance (or until relapse/progression, unacceptable toxicity or death whichever occurs first) in follicular lymphoma patients who have responded to an induction treatment with rituximab.



SELECTION OF PATIENTS

Follicular lymphoma patients with measurable disease according to Cheson (1), not transformed and without cardiac or other major illness, without anti-tumor therapy in the last 30 days.

TRIAL DURATION

The expected accrual duration into the induction treatment is 3 years. Another 5 years of follow-up period are expected for the observation of the required number of events. Randomized patients will be followed up for 10 years.

TRIAL TREATMENT

Induction:		rituximab 375 mg/m^2 weekly x4
Maintenance:	Arm A:	rituximab 375 mg/m^2 every 2 months x4
	Arm B:	rituximab 375 mg/m^2 every 2 months for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity or death whichever occurs first.

DOCUMENTATION

- Eligibility Form (E)
- On-Study Form (A)
- Re-Staging Form (B)
- Randomization Form (R)
- Maintenance Form (M)
- Tumor Assessment Form (T)
- Treatment Summary Form (C)
- Follow-up Form (F)
- Serious Adverse Event Form (SAE)

2 INTRODUCTION AND BACKGROUND

2.1 Disease and therapy background

Follicular lymphoma is a low-grade lymphoma and patients experience a median survival of nine years. In the WHO classification it is further classified into grade 1, 2 or 3, depending on the percentage of large cells seen on high power field microscopy. Biologically it is characterized by the presence of a t(14;18) translocation causing an overexpression of bcl-2 oncogene. Clinically its evolution is characterized in general by an indolent phase lasting several years, in which the disease is usually sensitive to several drugs such as alkylating agents, prednisone, anthracyclines, vinca alcaloids, purine analogues and monoclonal antibodies such as rituximab (2,3,4). When a first remission is obtained by chemotherapy, it lasts for a median time of 3 years, while the second remission lasts only a median of 1.5 years and further remissions only 6 months approximately. In 1/3 of the cases, follicular lymphoma eventually transforms to a high-grade pattern, responding then only to combination chemotherapies usually employed for high-grade disease, such as anthracyclines or Ara-C containing regimens or high-dose chemotherapy with autologous stem cell transplantation. Follicular lymphoma remains a disease considered to be incurable except for the few cases, which are diagnosed at a very early stage. Radiotherapy is also a treatment option for these patients and is usually applied to either involved field in very early stages or to palliate tumor masses, which are causing symptoms.

2.2 Therapy with rituximab

Monoclonal antibodies have considerably changed the treatment of patients with follicular lymphoma. This class of drugs, the most used of which is the anti-CD20 antibody rituximab, showed to induce remission in a high proportion of patients, including those who did not respond to chemotherapy (5). The combination of rituximab with chemotherapy significantly improved the response rate and the survival of patients with lymphoma (6). Rituximab is usually very well tolerated and, apart from infusion-related symptoms at first administration, it causes very few side effects and is well accepted by patients. Rituximab monotherapy produces a response rate of approximately 50% in pre-treated patients and of 65% in chemotherapy-naive patients. The median EFS (from the first induction infusion to disease progression/relapse/death) was 12 months (10 months in SAKK 35/98) in pre-treated and 18 months (19 months in SAKK 35/98) in previously untreated patients. These results, as shown in a previous SAKK trial, improved to 15 months and 36 months respectively without any increase in toxicity, if a 4-times maintenance treatment with rituximab is given (7).

2.3 Available results and toxicity of trial treatment

The analysis of the previous trial SAKK 35/98 showed that after rituximab monotherapy given at the standard dose and schedule (375 mg/m^2 weekly x 4), a further maintenance treatment of 375 mg/m^2 every 2 months x 4 can significantly prolong the EFS and increase the proportion of patients remaining in remission at 12 months, both assessed by clinical and molecular-biological criteria. This effect is mainly due to maintaining remission in patients with partial response. In other words, the prolonged rituximab administration prevents responding patients who still have detectable disease from progressing. The maintenance is administered without an increased incidence of side effects. The analysis also showed that this maintenance effect was limited almost only to patients who had responded to rituximab induction, while it was practically absent in patients with only stable disease at 12 weeks after starting rituximab induction.

2.4 Pharmacology of trial drug

Rituximab is an anti-CD20 chimeric antibody, with a murine variable region and a humanized constant component. Its pharmacokinetics presents a peek lasting a few hours after infusion, then dropping to 0 within a week in a few patients but remaining at measurable levels in the majority. Repeated infusions at one-week interval obtain an increase of the peak level and after the fourth infusion measurable levels of rituximab are found after 2 and 3 months in the serum of the majority of cases. A significant correlation has been found between the level of plasma drug concentration at different times after treatment and the amplitude of response, suggesting that patients with higher and prolonged serum rituximab level have a higher chance of responding (8).

2.5 Rationale for performing the trial

The above-mentioned serum level / response correlation was the main rationale for performing the SAKK 35/98 trial. That trial confirmed that a prolonged exposure to rituximab improved clinical results in terms of EFS, response duration and proportion of patients with follicular lymphoma still in response at one year. The results of that trial suggest that rituximab could delay lymphoma growth in patients with measurable persisting disease after responding to the first rituximab treatment. We therefore hypothesize in this trial that a continued exposure to rituximab could further increase the EFS. This trial is thus designed to compare the maintenance schedule for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity, or death whichever occurs first.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective

The main objective of this trial is to investigate if efficacy with maintenance rituximab for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity or death whichever occurs first, is superior to 4 times maintenance with rituximab.

3.1.2 Secondary objectives

The secondary objectives of the trial are to assess:

- the safety of the two schedules
- pharmaeconomical aspects
- evolution of immunologic competence

3.2 Endpoints

For definition see section 13 (Criteria of evaluation and definitions)

3.2.1 Primary endpoint

- event-free survival (EFS)

3.2.2 Secondary endpoints

- progression-free survival
- overall survival
- objective response
- adverse reactions during and after maintenance treatment
- prognostic value of of baseline CRP
- molecular remission (for Swiss centers only)
- duration of molecular remission (for Swiss centers only)
- evolution of immunologic competence (for Swiss centers only)

3.2.3 Pharmaeconomical analysis

The totality of substantial direct costs incurred with the treatment.

3.2.4 Molecular biology

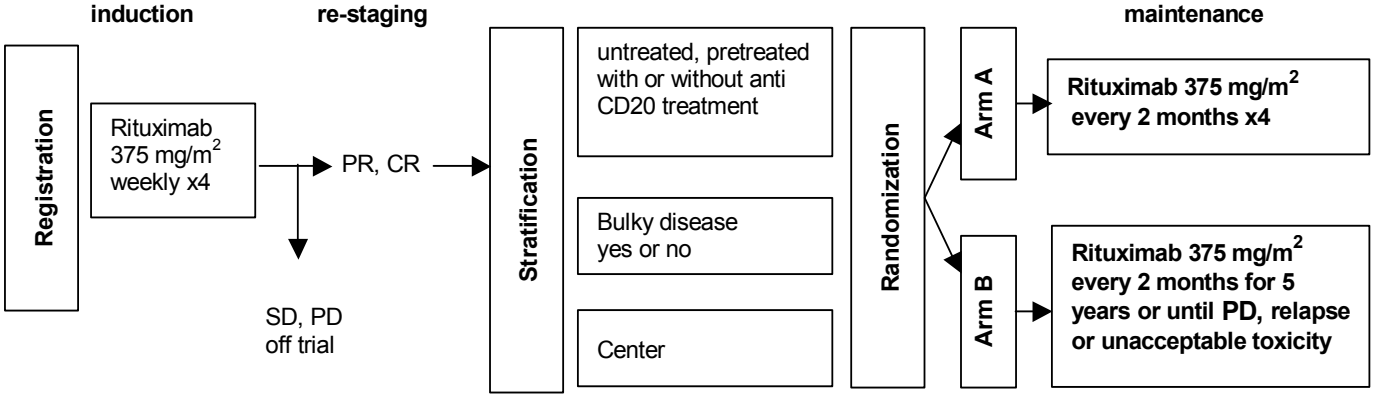
The absence of t(14;18) positive cells in peripheral blood and bone marrow.

3.2.5 Immunophenotyping

The relative and absolute counts of lymphocyte subpopulations (B lymphocytes, CD4 T lymphocytes, CD8 T lymphocytes, NK cells).

4 TRIAL DESIGN

This is an open, randomized, multicenter phase III trial comparing two different schedules of rituximab maintenance.



5 TRIAL DURATION AND TERMINATION

The inclusion of patients for induction treatment will start in Q1 2004 and stop after inclusion of 270 patients that is expected in Q2 2007, i.e., 90 induction patients/year.

We assume that approximately 50% patients will achieve CR or PR after induction treatment, i.e., 45 patients will be randomized per year.

All randomized patients will be followed up for 10 years after randomization.

The trial may be closed prematurely based on results of one of the two planned interim analyses (see section “statistical considerations”).

The trial might be terminated prematurely if new scientific data become available which change the risk/benefit assessment.

If accrual is lower than 30 registered patients per year after a run-in phase of 6 months, the continuation of the trial will be discussed in the Scientific Committee.

6 SELECTION OF PATIENTS

For timelines of procedures and evaluations see section 12.

6.1 Inclusion criteria for registration

6.1.1 Patients must have histologically confirmed follicular lymphoma grade 1, 2, 3, 3a or 3b (according to WHO, see appendix VIII).

6.1.2 CD20 expression on immunohistochemistry.

6.1.3 Any of the following disease status:
– untreated
– relapsed/progressed
– chemotherapy resistant disease
– stable disease (last administration of the last systemic treatment must be at least 12 weeks before registration).

6.1.4 Patients previously treated with rituximab or radiolabelled anti CD-20 therapy (either alone or in combination with cytostatics) must have responded to the anti CD-20 containing regimen (CR or PR).
At least 12 months must have elapsed from the last anti CD-20 therapy administration.

6.1.5 Patients must have at least one two-dimensionally measurable lesion with greatest transverse diameter ≥11 mm in CT scan (MRI is allowed only if CT scan cannot be performed).

6.1.6 Patients must give written informed consent before registration.

6.1.7 Patients must have the capability to understand information given by the investigator on the trial.

6.1.8 Age must be ≥18 years.

6.1.9 Performance status must be ≤2 on the WHO scale (see appendix X).

6.1.10 Adequate cardiac function (EF ≥50%) as assessed by echocardiography or MUGA scan.

6.1.11 Patient compliance and geographic proximity that allow proper staging and follow-up.

6.1.12 Women are not breast feeding, are using effective contraception if sexually active, are not pregnant and agree not to become pregnant during participation in the trial and during the 12 months thereafter. A negative pregnancy test is required for women in childbearing age.
Men agree not to father a child during participation in the trial and during the 12 months thereafter.

6.2 Exclusion criteria for registration

6.2.1 Patients with prior or concomitant malignancies, except non-melanomatous skin cancer or adequately treated in situ cervical cancer.

6.2.2 Presence or history of CNS disease (either CNS lymphoma or lymphomatous meningiosis).

6.2.3 Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. acute or ongoing infection, HIV-infection, uncontrolled diabetes mellitus, active autoimmune disease).

6.2.4 Transformation to high-grade lymphoma (secondary to “low-grade” FL).

6.2.5 Patients regularly taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to ≤20 mg/day prednisone for indications other than lymphoma or lymphoma-related symptoms.

6.2.6 Systemic tumor therapy in the last 30 days.

6.2.7 Treatment in a clinical trial within 30 days prior to trial entry.

6.3 Inclusion criteria for randomization

6.3.1 The patient has received 4 doses of rituximab infusion according to protocol.

6.3.2 At least 11 weeks have elapsed from start of rituximab induction therapy.

6.3.3 All lesions reported in the On-Study Form have been re-evaluated at restaging.

6.3.4 Patient must have reached a PR or CR at restaging (according to appendix IX).

6.4 Exclusion criteria for randomization

6.4.1 Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial.

7 REGISTRATION / RANDOMIZATION

7.1 Registration

Prior to registration, the following steps have to be performed:

- Check the eligibility criteria
- Obtain informed consent from the patient
- Fill in the Eligibility Form (Form E)
- Fax the completed, dated and signed Form E to

SAKK Trials Office at the SIAK Coordinating Center
Effingerstrasse 40
CH - 3008 Bern
Fax. +41 31 389 92 00 / Tel. +41 31 389 91 91

If all data are provided legibly and complete, registration shall be confirmed by fax within one hour (opening hours: Monday to Friday 8:00 a.m. to 5:00 p.m.)

Induction therapy has to be started within 7 days from registration.

The SAKK Trials Office will be closed on the following dates

- 1st January
- 2nd January
- Good Friday (Friday before Easter)
- Easter Monday
- Ascension Thursday
- Whit Monday
- 1st August
- 24th December (from 12 a.m.)
- 25th December
- 26th December
- 31st December (from 12 a.m.)

7.2 Randomization

Prior to randomization the following steps have to be performed:

- Re-evaluate all lesions reported at registration by the same mean
- Check the eligibility criteria for randomization and fill in the Randomization Form (Form R).
- Fax the completed, dated and signed Form R to the SAKK Trials Office: Fax. +41 31 389 92 00 (Opening hours Monday to Friday 8:00 a.m. to 5:00 p.m.).

Randomization is stratified according to the following factors, assessed at registration:

- Treatment status: Untreated, pretreated with or without anti-CD20 therapy. Patients having received radiotherapy only, are considered as therapy-naïve. Patients previously treated with CD-20 containing regimen - either alone or in combination - must have responded to the anti CD-20 containing regimen. At least 12 months must have elapsed from the last CD-20 containing regimen administration.
- Bulky disease at registration: yes or no. (Definition of bulky: a mass or lymph node conglomerate **≥** 5 cm diameter)
- Center

At randomization eligible patients will be randomized in a 1:1 fashion to one of the two arms:

arm A: rituximab 375 mg/m^2 every 2 months x4

arm B: rituximab 375 mg/m^2 every 2 months for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity or death.

Maintenance therapy has to be started within 7 days from randomization.

8 DRUG SUPPLY

8.1 Supply of rituximab

Rituximab will be prescribed for those patients who are treated for a disease where the marketing authorization and reimbursement of the insurances are granted.

For patients treated for diseases not included in the marketing authorization, rituximab will be provided free of charge by the local Roche affiliate.

8.1.1 Drug supply in Switzerland

Rituximab for induction therapy will be prescribed for all relapsed patients, according to the current marketing authorization. In case a new marketing authorization is granted, rituximab will be prescribed for patients treated within this indication.

Trial treatment will be provided free of charge by Roche Pharma (Schweiz) AG, Reinach for the maintenance therapy and for the induction therapy in patients with newly diagnosed follicular lymphoma.

The SAKK Trial Coordinator will order an initial stock of the drug (5 vials of 500 mg and 10 vials of 100 mg) for each participating center upon receipt of the ethics approval. Additional rituximab has to be ordered directly by the center at Roche Pharma (Schweiz) AG when the stock is nearly finished. All drug requests should be made with the specific drug order form at least one week ahead of the date that new supplies are required at the center. The drug order form will be made available to local data managers and can be downloaded from www.siak.ch (members section).

Responsible at Roche Pharma (Schweiz) AG:

Dr. med. Marius Komarek
Medical Manager Oncology
Roche Pharma (Schweiz) AG
Schönmattstr. 2
CH-4153 Reinach
Tel: ++41 61 715 43 61 Fax: ++41 61 715 42 70
e-mail: marius.komarek@roche.com

8.1.2 Drug supply outside of Switzerland

The local Roche affiliate and investigators of each participating country are responsible to negotiate and arrange drug supply.

8.1.3 Labeling

Trial medication will be labeled on the box and on the vial as follows:

Protocol SAKK 35/03
rituximab (Mabthera®)
FOR CLINICAL TRIAL USE ONLY
Free of charge
UPN ☐☐☐ / Initials ☐☐ ☐
Date of Birth ☐☐ ☐☐ ☐☐☐☐

8.1.4 Dispensing and accountability of rituximab

Please ensure the use of the drug inventory log (appendix XVI), which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, UPN). If an institution already has its own accounting system, it may be used instead of the SAKK drug

inventory log only after inspection and approval by the SAKK monitor.

The UPN, initials and date of birth of the patient have to be written on the label of the package as soon as the package is opened.

The monitor will check the inventory log.

8.1.5 Handling and Security

Rituximab is a mouse/human (gamma 1, kappa) antibody, produced by a Chinese hamster ovary transfectoma. The antibody is formulated for intravenous infusion as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. The product must be stored in a refrigerator at 2-8 °C.

Rituximab is packaged in 10 ml (100 mg) and 50 ml (500 mg) pharmaceutical grade glass vials at a concentration of 10 mg protein per ml, 1 vial per package.

Information on handling and safety can be found in the product information.

9 TRIAL TREATMENT

9.1 Induction phase

Treatment with rituximab should start within 7 days from registration. Rituximab 375 mg/m^2 should be given according to the guidelines for administration of rituximab (see appendix XII) once a week for 4 weeks. The interval between each administration should be of 7 +/-1 day.

9.2 Maintenance for trial arm A

Treatment with rituximab should start within 7 days from randomization. Rituximab 375 mg/m^2 should be given according to guidelines for administration (see appendix XII) every 2 months (range 8 to 10 weeks) for 4 times.

9.3 Maintenance for trial arm B

Treatment with rituximab should start within 7 days from randomization. Rituximab 375 mg/m^2 should be given according to guidelines for administration (see appendix XII) every 2 months (range 8 to 10 weeks) for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity or death whichever occurs first

9.4 Concomitant/supportive therapy

The first rituximab infusion must be given at a slower infusion rate according to the guidelines in appendix XII. The patient should be kept on observation during the first rituximab administration and for at least 2 hours after the end of the infusion. In case patients develop infusion related symptoms it is recommended to admit them in hospital overnight for the treatment of possible late systemic side effects.

Prior to the first rituximab application, pretreatment with allopurinol 300 mg daily orally is mandatory. In case of hyperuricaemia, allopurinol will be applied according to each participating center's policy.

9.5 Prohibited Medications

The administration of corticosteroids for the prevention or treatment of side effects is forbidden (not to influence the remission rate), except in case of acute life-threatening side effects.

9.6 Treatment duration

Patients in arm A will be treated up to a maximum of 4 rituximab maintenance administrations while patients in arm B will keep receiving the drug every 2 months to a maximal duration of 5 years or until progression/relapse, unacceptable toxicity or death, whichever occurs first.

Trial treatment will be stopped and patients will be transferred to the follow-up phase as soon as one of the following event is observed:

- progressive disease or relapse (see definitions, appendix IX).
- unacceptable toxicity (e.g. worsening of the cardiac function with ejection fraction < 50%)
- initiation of non-protocol anticancer treatment or concomitant steroids introduced because of lymphoma symptoms or concomitant radiotherapy
- patient refusal to continue participation (any effort should be undertaken to follow-up the

patient)

- intercurrent illness that prevents further administration of rituximab
- any case of grade ≥ III non-hematologic toxicity/adverse reactions other than infusion-related symptoms
- any grade IV hematologic toxicity/adverse reactions (possibly, probably or definitively related to rituximab)
- patient becomes pregnant
- secondary malignancy
- if the continuation would not be in the best interest of the patient

During the follow-up period data specified in section 12 will be collected.

10 TOXICITY AND PROCEDURES FOR ADVERSE EVENTS

10.1 Toxicity of rituximab

The main side effect is the appearance of infusion-related symptoms during the first administration, in about 1/3 of patients. Most frequent side effects are fever and shivering (rigors); less frequent are hypotension, dyspnea and nausea.

In a few patients with a previous history of cardiac disease a sudden and unexplained worsening of the cardiac function was observed, but in patients with stable cardiac disease and an ejection fraction > 50% no such cases were described.

In the previous trial SAKK 35/98 an incidence of 16.6% grade 3/4 neutropenia was observed at visits between randomization and week 52 in patients receiving maintenance treatment. This incidence was comparable to 15.9% observed in patients without maintenance treatment. In addition, an important decrease in circulating B-cells at week 52 was described but without an increased rate of infections, when compared with patients without maintenance treatment.

Treatment with rituximab prolonged over a time longer than 2 years has never been applied, so that particular attention should be paid to any possible side effects over an extended time period, including infections, cardiac problems, respiratory problems and incidence of second tumors.

10.2 Procedures for adverse events

10.2.1 Warnings and precautions

If a patient experiences serious infusion-related side effects during the first administration, the infusion of the drug should immediately be stopped and anti-histamine and paracetamol should be given to the patient. In case of severe shivering and rigors, the patient can be treated by 25 to 50 mg of pethidine intravenously. In case of very severe reactions including severe dyspnea, hypotension or heart problems not readily solved by infusion interruption, intravenous corticosteroids could be exceptionally administered. See administration guidelines in appendix XII.

10.2.2 Procedure for non-hematologic toxicity

No dose modifications are planned. In case of grade ≥ III toxicity/adverse reactions (possibly, probably or definitively related to rituximab) other than infusion-related symptoms, the patient should be transferred to the follow-up phase.

10.2.3 Procedure for hematologic toxicity

No dose modifications are planned. In case of grade IV toxicity/adverse reactions (possibly, probably or definitively related to rituximab) the patient should be transferred to the follow-up phase.

10.3 Safety parameters

10.3.1 Renal function

Serum creatinine

10.3.2 Liver function

Bilirubin, AP, ASAT or ALAT

10.3.3 Hematological function

Hemoglobin, WBC, neutrophils, monocytes, lymphocytes, thrombocytes

10.3.4 Cardiovascular

Blood pressure, ECG, Left ventricular ejection fraction (echocardiography or MUGA)

11 COLLECTION AND REPORTING OF ADVERSE EVENTS (AEs) AND SERIOUS ADVERSE EVENTS (SAEs)

11.1 Definition of adverse event

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may NOT be considered related to the medical treatment or procedure.

11.2 Collection of AEs

Patients will be instructed by the investigator to report the occurrence of any unfavorable symptom, sign, or disease (AE).

The investigator (treating physician) is asked to verify absence or presence of all AEs predefined on the case report forms of a specific trial at baseline and during the trial. Information in the medical file has to be provided in the CTCAE coding system. They should not be given in a narrative description.

11.3 Reporting of AEs

The NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) are applied for reporting AEs. NCI CTCAE v3.0 (as pdf) and instruction how to use NCI CTCAE v3.0 can be found on http://ctep.info.nih.gov/reporting/ctc.html.

Hardcopies can be requested at the SAKK Trials Office. CTCAE will not be incorporated into the protocol, but a quick reference guide is incorporated (see below).

11.3.1 AE categories in the CTCAE

The CTCAE, v3.0 includes 28 categories of adverse events with more than 900 individual adverse events.

The primary organization of the CTCAE, v3.0 is based on pathophysiological (e.g., Allergy/Immunology) and anatomical (e.g., Dermatology/Skin) categories to facilitate location of related adverse events. The following is a list of categories of adverse events in the CTCAE, v3.0.

ALLERGY/IMMUNOLOGY
AUDITORY/EAR
BLOOD/BONE MARROW
CARDIAC ARRHYTHMIA
CARDIAC (GENERAL)
COAGULATION
CONSTITUTIONAL SYMPTOMS
DEATH
DERMATOLOGY/SKIN
ENDOCRINE
GASTROINTESTINAL
GROWTH AND DEVELOPMENT
HEMORRHAGE
HEPATOBILIARY/PANCREAS
INFECTION
LYMPHATICS
METABOLIC/LABORATORY
MUSCULOSKELETAL/SOFT TISSUE
NEUROLOGY
OCULAR/VISUAL
PAIN
PULMONARY/UPPER RESPIRATORY
RENAL/GENITOURINARY
SECONDARY MALIGNANCIES
SEXUAL/REPRODUCTIVE FUNCTION
SURGERY/INTRA-OPERATIVE INJURY
SYNDROMES
VASCULAR

An **AE** is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

AEs are listed alphabetically within CATEGORIES, and each AE term is mapped to a MedDRA v6.0 term and code.

A **supra-ordinate term** is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs (*'Select'* terms) that are all related to the supra-ordinate term. Supra-ordinate terms are new in CTCAE v3.0 and they provide clustering of related events and consistent representation of Grade (severity). Supra-ordinate terms are not AEs, are not mapped to a MedDRA v6.0 term and code, and cannot be used for reporting.

11.3.2 Grading of AEs

Grade refers to severity of the AE. CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE

Grade 2 Moderate AE

Grade 3 Severe AE

Grade 4 Life-threatening or disabling AE

Grade 5 Death related to AE

Note:

- Any treatment-related adverse event experienced by a patient is graded using the specific adverse event terms listed in the NCI CTCAE.
- Grading is not modified based on a patient's condition at baseline.
- If a given adverse event is experienced more than once during a cycle, only the grade associated with the most severe adverse event is reported.
- Adverse events not included in the NCI CTCAE, v3.0 should be reported and graded under the "Other" adverse event within the appropriate category and graded 1 to 5 according to the general grade definitions provided above.
- Most adverse events and grading criteria are applicable to any treatment modality. Some are specified for a particular modality. The most relevant adverse event should be used to grade adverse events. When it is not possible to determine whether one or both contributed, use the most relevant description of the adverse event.
- All adverse events considered to be related to the treatment, regardless of severity, will be followed up by the investigator until satisfactory resolution or definitive permanent sequelae.
- **Disease progression or signs and symptoms definitely related to disease should not be reported. Objective documentation of progression should always be sought. However, all AEs for which other etiology than disease progression cannot be excluded, should be reported.**
- Treatment delivery system malfunctions (e.g. occlusion of port-a-cath or problems with peripheral vein access) should not be graded as adverse events.

11.3.3 Scale for attribution of adverse event / causality assessment

Assign attribution of each adverse event using the following criteria:

1 = Unrelated The adverse event is *clearly not related* to the investigational agent(s). The AE is completely independent of trial treatment and/or evidence exists that the event is definitely related to another etiology.

2 = Unlikely The adverse event is doubtfully related to the investigational agent(s). Temporal association between the AE and the study product and the nature of the event is such that the study product is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible)

3 = Possible The adverse event may be related to the investigational agent(s). Less clear temporal association; other etiologies also possible.

4 = Probable The adverse event is likely related to the investigational agent(s). Clear-cut temporal association and a potential alternative etiology is not apparent.

5 = Definite The adverse event is clearly related to the investigational agent(s). Clear-cut temporal association, and no other possible cause.

11.4 Definition of serious adverse events (SAEs)

A serious adverse event includes any of the events below:

	Comments
Fatal	Includes all deaths up to 30 days after cessation of treatment. Deaths occurring later are only to be considered as SAE if they are possibly, probably or definitely related to treatment.
Life-threatening	The patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.
Requires inpatient hospitalization	Events not considered to be serious adverse events are hospitalizations occurring under the following circumstances: • elective surgery (planned before entry into the trial) • **for treatment or observation of infusion related symptoms** • occurring on an outpatient basis and do not resulting in admission • are part of the normal treatment or monitoring of the trial treatment • progressive disease
Prolonged hospitalization	
Disabling	Includes persistent or relevant disability or incapacity occuring during or after treatment.
Overdosage	Defined as the accidental or intentional application of any dose of a product that is considered both excessive and medically important, even if no event occurred that would have to be classified as SAE per se.
Second primary cancer	Any new malignancy other than a relapse/progression of the current tumor.
Congenital anomaly	Birth defect of offspring.
Grade 4 AE	All grade 4 AEs
Other medically significant condition	

All the events listed in the table above have to be reported during trial treatment (induction and maintenance therapy) and up to 30 days after treatment termination.

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: June 10, 2003

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word '*Select*' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

11.4.1 SAEs after end of trial treatment

During the follow-up phase (starting 30 days after treatment termination), the following events have to be reported as SAE:

- fatalities and severe events possibly, probably or definitely related to late effects of therapy
- disabling events
- second primary cancer
- congenital anomaly

11.5 Reporting of SAEs to the SAKK Trials Office and the local Ethics Committee

Any SAE must be reported by faxing the completed **section A** of the SAKK SAE Form within 24 hours (working days) to:

SAKK Trials Office at the SIAK Coordinating Center
Effingerstrasse 40
CH – 3008 Bern
Fax: +41 31 389 92 00

The SAE outcome must be reported within 2 weeks after onset by completing and faxing or mailing **section B** of the SAKK SAE form. In case the SAE is reported as ongoing after 14 days, section B has to be sent again with the final outcome.

Ethics committees must be informed by the investigator about local SAEs according to the VKlin/OClin and local regulations.

The originals of the SAE forms (both sections A and B) must be sent to the SAKK Trials Office. The centers keep a copy for their own records.

11.6 Periodic reporting on safety to centers

Legislation requires that the sponsor informs investigators in multicenter trials about all SAE that might be related to treatment and further safety relevant issues.

Therefore monthly reporting of individual SAEs related to the treatment are provided to each principal investigator (can be downloaded from www.siak.ch (members section).

A yearly safety summary is provided by the SAKK Safety Office to Swissmedic and to the local investigators for forwarding to the ethics committees.

12 EVALUATIONS AND INVESTIGATIONS BEFORE, DURING AND AFTER TRIAL TREATMENT

Schedule of evaluations and investigations see appendix XI.

12.1 Evaluations and procedures prior to registration

- histological confirmation of follicular lymphoma (according to WHO grading system, appendix VII)
- CD20+ determination by immunohistochemistry

To be performed within 3 months prior to registration:

- bone marrow aspirate and trephyne biopsy.
  In case bone marrow is involved, biopsy must be repeated within 3 weeks prior to registration for collection of bone marrow for the translational study **(Swiss centers only)**.

To be performed within 3 weeks prior to registration:

- informed consent (must be signed prior to any protocol specific procedure)
- medical history: incl. investigation of all eligibility criteria, baseline symptomes and previous therapy for follicular lymphoma
- physical examination (including performance status)
- cardiac ejection fraction by echocardiography or MUGA scan
- lab hematology: hemoglobin, WBC, neutrophils, monocytes, lymphocytes, thrombocytes
- lab biochemistry: calcium, AP, ASAT or ALAT, bilirubin, creatinine
- serum immunoglobulin IgA, IgG, IgM
- pregnancy test (if applicable)
- C-reactive protein (CRP)
- erythrocyte sedimentation rate (ESR)
- LDH
- description of the nodal and extranodal localizations of disease
- staging of **measurable disease**: CT (neck, thorax, abdomen, pelvis). MRI is allowed only if CT scan cannot be performed
- staging of **evaluable disease**: CT, MRI, ultrasound and PET may be used

- collect 3-4 ml peripheral blood into an EDTA tube and send to Aarau for the determination of lymphocyte subpopulations (see section 18) **(Swiss centers only)**
- collect heparinized blood (20 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) **(Swiss centers only)**
- collect heparinized bone marrow (2-3 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) **(Swiss centers only)**.
  In case previous bone marrow analysis (within 3 months prior to registration) revealed no involvement of bone marrow, collection may be omitted.

12.2 Restaging

Must be performed between 11 and 13 weeks after the first rituximab administration and before randomization:

- medical history (including all eligibility criteria)
- physical examination (including performance status)
- lab hematology: Hemoglobin, WBC, neutrophils, monocytes, lymphocytes, thrombocytes
- lab biochemistry: calcium, AP, ASAT or ALAT, bilirubin, creatinine
- serum immunoglobulin IgA, IgG, IgM
- LDH
- ESR
- bone marrow aspirate and trephyne biopsy (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline)
  staging of **measurable disease**: CT (neck, thorax, abdomen, pelvis). MRI is allowed only if CT scan cannot be performed
- staging of **evaluable disease**: CT, MRI, ultrasound and PET may be used

- collect 3-4 ml peripheral blood into an EDTA tube and send to Aarau for the determination of lymphocyte subpopulations (see section 18) **(Swiss centers only)**
- collect heparinized blood (20 ml) and send to Bellinzona for determination of t(14;18) (only if positive for t(14;18) at baseline) **(Swiss centers only)**
- collect heparinized bone marrow, 2-3 ml and send to Bellinzona for the determination of t(14;18) (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline) **(Swiss centers only)**

12.3 Evaluation during trial maintenance treatment

To be performed:

- Arm A up to **month 6** or until an event occurs.
- Arm B up to **5 years after randomization** or until an event occurs.

These events are defined in section 13.1 (event-free survival):

Every 2 months:

- physical examination (including performance status)
- medical history including adverse events
- hemoglobin, WBC, neutrophils, monocytes, lymphocytes, thrombocytes

Every 6 months after randomization:

- LDH
- serum immunoglobulin IgA, IgG, IgM
- staging of **measurable disease**: CT (neck, thorax, abdomen, pelvis). MRI is allowed only if CT scan cannot be performed
- staging of **evaluable disease**: CT, MRI, ultrasound and PET may be used

- collect 3-4 ml peripheral blood into an EDTA tube and send to Aarau for the determination of lymphocyte subpopulations (see section 18) **(Swiss centers only)**

Every 12 months after randomization:

- bone marrow aspirate and trephyne biopsy (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline)

- collect heparinized blood (20 ml) and send to Bellinzona for determination of t(14;18) (if positive for t(14;18) at baseline) **(Swiss centers only)**
- collect heparinized bone marrow, 2-3 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline) **(Swiss centers only)**

At clinical relapse/progression:

- bone marrow aspirate and trephyne biopsy (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline)

- collect heparinized blood (20 ml) for determination of t(14;18) (only if involved at baseline **(Swiss centers only)** and send to Bellinzona
- collect heparinized bone marrow, 2-3 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline) **(Swiss centers only)**

12.4 Evaluation during follow-up phase

Evaluations in the follow up phase are different between patients without relapse/progression and those with relapse/progression.

All patients will be followed up for 10 years after randomization.

12.4.1 Patients without relapse/progression

For patients without an event in both arms should be assessed at the predefined intervals in order not to risk biasing detection of disease progression.

Every 3 months:

- physical examination (including performance status)
- medical history

Every 6 months:

- **for measurable disease**: CT (neck, thorax, abdomen, pelvis). MRI is allowed only if CT scan cannot be performed.
- **for evaluable disease**: CT, MRI, ultrasound and PET may be used
- serum immunoglobulin IgA, IgG, IgM
- LDH

- collect 3-4 ml peripheral blood into an EDTA tube and send to Aarau for the determination of lymphocyte subpopulations (see section 18) **(Swiss centers only)**

Every 12 months:

- bone marrow aspirate and trephyne biopsy (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline)

- collect heparinized blood (20 ml) for determination of t(14;18) (only if involved at baseline

(Swiss centers only) and send to Bellinzona

- collect heparinized bone marrow, 2-3 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline) **(Swiss centers only)**

At clinical relapse/progression:

- bone marrow aspirate and trephyne biopsy (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline)

- collect heparinized blood (20 ml) for determination of t(14;18) (only if involved at baseline tion **(Swiss centers only)** and send to Bellinzona
- collect heparinized bone marrow, 2-3 ml) and send to Bellinzona for the determination of t(14;18) (see section 17) (only if infiltrated by lymphoma cells or positive for t(14;18) at baseline) **(Swiss centers only)**

12.4.2 Patients with relapse/progression

Every 12 months:

Only the survival status, further antitumor therapy and late toxicities must be assessed.

Patients will be followed up for 10 years after randomization.

13 CRITERIA OF EVALUATION AND DEFINITIONS

13.1 Event-free survival (EFS)

Event-free survival is defined as the period from randomization for the maintenance until one of the following events occur:

- progressive disease or relapse (see definitions, appendix IX)
- unacceptable toxicity (e.g. life-threatening or serious event which is probably, possibly or definitively related to the trial treatment; e.g. worsening of the cardiac function with ejection fraction < 50%, any case of grade ≥ III non-hematologic toxicity/adverse reactions other than infusion-related symptoms, any grade IV hematologic toxicity/adverse reactions)
- death from any cause
- initiation of non-protocol anticancer treatment or concomitant steroids introduced because of lymphoma symptoms or concomitant radiotherapy
- secondary malignancy

13.2 Progression-free survival

Time from randomization to relapse/progression/death from NHL, whichever occurs first (for all randomized patients).

13.3 Overall survival

Overall survival will be calculated from randomization until death from any cause. Causes of death will be recorded and monitored, in particular death without relapse or progression.

13.4 Objective response

Complete (CR), complete unconfirmed (CRu), partial responses (PR), stable disease (SD), relapse and progressive disease (PD) are assessed following the criteria of Cheson et al, 1999 (1) (see appendix IX).

13.5 Adverse reactions during and after maintenance therapy

Assessed according to the NCI-CTCAE v3.0 grading during and after maintenance therapy.

13.6 Prognostic value of baseline CRP

CRP will be determined at baseline. The aim is to evaluate if an elevated CRP at study entry correlates with impaired prognosis in terms of progression-free and event-free survival.

13.7 Molecular remission (for Swiss centers only)

Blood: The absence of t(14;18) positive cells in blood, in patients with a positive result before registration, after induction treatment with rituximab, at 6 and 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until relapse/progression.

Bone marrow: The absence of t(14;18) positive cells in bone marrow, in patients with a positive

result before registration, after induction treatment with rituximab, at 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until relapse/progression.

13.8 Duration of molecular remission (for Swiss centers only)

Calculated from the first demonstration of t(14;18) negativity in bone marrow and peripheral blood until the demonstration of t(14;18) positivity for patients who were positive prior to registration.

13.9 Evolution of immunologic competence (for Swiss centers only)

Cellular: the evolution over time of the concentration of B-lymphocytes, CD4 lymphocytes, CD8 T lymphocytes and natural killer cells in the peripheral blood.

Humoral: the evolution over time of the concentration of IgG, IgA and IgM in the blood.

13.10 Pharmaeconomical analysis (for Swiss centers only)

See section 19

14 STATISTICAL CONSIDERATIONS

14.1 Introduction

The main objective of the trial is to compare EFS (defined in section 13.1) between 4 times maintenance treatment and maintenance for a maximal duration of 5 years or until relapse/progression, unacceptable toxicity or death. It is expected that patients receiving maintenance until relapse/progression will have a better EFS than those receiving 4 times maintenance.

14.2 Sample size estimation

Based on results of SAKK 35/98, the following design parameters are used:

- Accrual rate = 90 induction patients/year,
- Response rate to induction treatment = 50%,
- Median EFS (calculated from date of randomization for the 4 times maintenance arm) = 2,5 years.

Enrollment into the induction phase is expected to last approximately 3 years, with a total of about 270 patients included for induction treatment. This implies that a total of about 135 patients will be randomized with an accrual rate of 45 randomized patients/year.

Prolonged maintenance for up to 5 years is considered worthwhile if EFS can be improved by at least 80%, i.e., median EFS 4.5 years.

In addition to the final analysis, two interim analyses are planned to allow early stopping of the trial if either the null hypothesis of no difference in EFS is rejected or the alternative hypothesis of an at least 80% improvement in EFS is rejected. An overall two-sided type I error probability of 5% and a statistical power of 80% are chosen for the log-rank test. The critical values for early stopping will be obtained using the O'Brien and Fleming boundary shape based on a spending function for the overall type I error probability (9) and a spending function for the overall type II error probability (10).

If the trial is not stopped early, a maximum of 99 events is required for the final analysis and is expected around 5.14 years after the last randomization, i.e., the expected trial duration is 3 years (accrual) + 5.14 years (follow-up) = 8.14 years.

Patients who are retrospectively found ineligible or non evaluable will not be removed from the trial nor replaced by new patients.

14.3 Criteria for early stopping

The two interim analyses will be carried out respectively about 2 years after enrollment of the first randomized patient and after having observed 60 events. The criteria for early stopping depend on the actual number of events at each interim analysis and will be obtained based on the O'Brien and Fleming boundary shape as mentioned above.

14.4 Evaluation

For registered patients, baseline characteristics as well as toxicity and efficacy of the induction treatment will be summarized by descriptive statistics for continuous variables and by frequency tables for categorical variables. For response rate to induction treatment a 95% confidence interval will be calculated and logistic regression may be used to explore the effects of baseline characteristics.

For randomized patients, all endpoints will be analyzed by intention-to-treat principle in the main trial. A second set of per-protocol analysis of efficacy endpoints will be performed after excluding patients with diagnosis other than FL or without measurable disease at baseline. For analyses of toxicity endpoints, only patients who have ever received trial treatment, no matter eligible or not, will be included.

Probabilities of time-to-event type endpoints will be estimated using Kaplan-Meier method and compared between arms using log-rank test. Medians and the associated 95% confidence intervals will be calculated. Cox regression will be performed to explore the effects of stratification factors and other covariates on probabilities of time-to-event type endpoints. If the assumption of proportional hazards cannot be justified, approaches other than log-rank test and Cox regression may be applied.

Contingency tables will be analyzed by chi-square or Fisher's exact test. Logistic regression may be used to explore effects of stratification factors and other covariates on binary endpoints. Continuous variables will be summarized by descriptive statistics and compared between arms by t-test or Wilcoxon rank sum test.

Mixed models may be applied for analyses of repeated measure data.

Reasons for missing values will be investigated if feasible. In case the assumption of missing at random is not justified, additional analyses taking into account the missing mechanism may be carried out.

15 DOCUMENTATION

Case report forms specifically created for this trial are used for documentation. It is very important to respect the schedule of visits prescribed in the protocol for all patients. All forms will be collected by the monitor.

The schedule for completing the different forms is presented in the following table

Form	**To be completed**	**To be submitted**
Form E (Eligibility Form)	Before registration	Fax before registration. The original will be collected by the monitor
Form A (On-Study Form)	At registration	Will be collected by the monitor
Form B (Restaging Form)	11-13 weeks after start of induction	Will be collected by the monitor
Form R (Randomization Form)	At randomization	Fax before randomization Original will be collected by the monitor
Form M (Maintenance Therapy Form)	Every 2 months from randomization at each rituximab infusion	Will be collected by the monitor
Form T (Tumor Assessment Form)	At re-staging, every 6 months from randomization until relapse/progression for a maximal duration of 10 years after randomization	Will be collected by the monitor
Form C (Treatment Summary Form)	At treatment stop of randomized patients	Will be collected by the monitor
Form F (Follow-up Form)	**For patients without relapse/progression:** Every 6 months up to 10 years after randomization **For patients with relapse/progression:** Every 12 months up to 10 years after randomization	Will be collected by the monitor
Serious Adverse Event Form (SAE)	Section A: To be completed and faxed within 24 hours Section B: Follow up report within 2 weeks	

Centers must use a patient enrollment and identification list in order to allow identification of a patient and proper usage of initials (see appendix XIV). This list must be kept at the center in the trial master file.

16 PATHOLOGY

16.1 Local pathology requirements

The local investigators of each center participating in this trial have to inform and to agree with the local pathologists about the protocol and in particular about data requested for the trial that are not collected per default.

16.1.1 Task for the local pathologist

The diagnosis of a follicular lymphoma must be made according to the criteria of the WHO classification (11). The histological examination of an involved lymph node or the affected extranodal organ respectively, is mandatory. Relapsed patients only need to be biopsied if a transformation of the lymphoma is suspected.

Histological diagnosis and lymphoma immunophenotyping by the primary local pathologist are sufficient for the patient to be entered into the trial. Determination of CD20 is mandatory. Examination of bone marrow only is not adequately diagnostic for lymphoma subtyping and does not fulfill the trial requirements.

There is no pathology review planned in this trial, however in case of doubt the histological material can be sent to the SAKK lymphoma review center for central review:

Dr. med. S. Cogliatti
Institute of Pathology
Cantonal Hospital of St. Gallen
CH – 9007 St. Gallen
Tel. +41 71 494 11 11
E-mail: sergio.cogliatti@kssg.ch

17 MOLECULAR BIOLOGY ANALYSIS

17.1 Introduction

Molecular response, as defined in follicular lymphoma by a t(14;18) PCR-negative status during the first year of therapy, is an important predictive factor for failure-free survival in follicular lymphoma. Within a population of 111 patients, five-year failure-free survival was 73% and 28% for molecular responders as defined by a negative PCR status within first year and nonresponders, respectively (P = 0.001) (12).

In the trial SAKK 35/98 64 out of 154 patients (42%) had PCR-detectable t(14;18) positive cells at baseline. Bone marrow was morphologically assessed in 64 patients, and 39 of these patients had an infiltration with FL cells. Paired blood and bone marrow samples were available for PCR analysis from 39 patients between weeks 8-12 after induction therapy with rituximab. Thirteen of these patients (33%) did not have PCR-detectable cells in blood and bone marrow, while 26 patients (67%) still had circulating t(14;18) positive cells in either bone marrow (8 patients), blood (1 patient), or both (17 patients). PCR negativity in blood and bone marrow in 13 patients was statistically significantly associated with partial or complete response after induction therapy with rituximab (P = 0.006) (13).

17.2 Objectives

Molecular response rate as defined by a negative PCR during or after treatment with rituximab in patients with a positive test at the baseline assessment.

17.3 Endpoints

Molecular response: PCR status after induction treatment with rituximab:

- in peripheral blood at 6 and 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until clinical relapse/progression.
- in bone marrow at 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until clinical relapse/progression or for a maximal period of 10 years after randomization.

17.4 Methods

Only patients registered at Swiss centers will be included into this project. All patients that provide informed consent for laboratory subprojects should participate in this subproject.

Molecular status in bone marrow and blood before, during and after treatment will be assessed by a PCR assay for the t(14;18)(q32;q21).

17.5 Sampling

17.5.1 Sampling time points

Within 21 days before registration

- 2-3 ml heparinized bone marrow
- 20 ml of heparinized blood

At restaging (after induction therapy)

- 2-3 ml heparinized bone marrow (only if initially involved, i.e. bone marrow infiltrated by lymphoma cells or positive for t(14;18) at baseline)
- 20 ml of heparinized blood (both arms: only if initially involved, i.e. peripheral blood positive for t(14;18) at baseline)

At 6 months since randomization

- 20 ml of heparinized blood (both arms: only if initially involved, i.e. peripheral blood positive for t(14;18) at baseline)

At 12 months since randomization

- 2-3 ml heparinized bone marrow (only if initially involved, i.e. bone marrow infiltrated by lymphoma cells or positive for t(14;18) at baseline)
- 20 ml of heparinized blood (both arms: only if initially involved, i.e. peripheral blood positive for t(14;18) at baseline)

Thereafter every 12 months until clinical relapse/progression in both arms (up to 10 years from randomization)

- 2-3 ml heparinized bone marrow (only if initially involved, i.e. bone marrow infiltrated by lymphoma cells or positive for t(14;18) at baseline)

- 20 ml of heparinized blood (both arms: only if initially involved, i.e. peripheral blood positive for t(14;18) at baseline)

At clinical relapse/progression in both arms up to 10 years from randomization

- 2-3 ml heparinized bone marrow (only if initially involved, i.e. bone marrow infiltrated by lymphoma cells or positive for t(14;18) at baseline)
- 20 ml of heparinized blood (both arms: only if initially involved, i.e. peripheral blood positive for t(14;18) at baseline)

No samples will be collected after clinical relapse/progression

17.5.2 Samples handling

After sample collection, the tube should be inverted immediately several times to ensure anticoagulation. No further handling (e.g., centrifugation) is required.

A local research nurse or a data manager must be responsible for collection and sending blood and bone marrow.

17.5.3 Sample shipping

The samples of each patient must be mailed immediately after collection. The tubes must be clearly labeled (SAKK 35/03, UPN, patients' initials, date of birth and date of blood or bone marrow drawn and shipped by EXPRESS (overnight express) AT ROOM TEMPERATURE, no later than on Thursday (to avoid arrival during weekend).

Francesco Bertoni, MD
Experimental Oncology
Oncology Institute of Southern Switzerland
c/o stabile IRB
via Vincenzo Vela 6
CH-6500 Bellinzona

Email: frbertoni@mac.com / phone: +41 (0)91 8200 367 / fax: +41 (0)91 8200 397

Address-stickers will be provided.

In case you have to draw blood on a Thursday or Friday, store samples at room temperature and send them as soon as possible.

The analysis will not be charged to the patient.

A cover letter is provided in appendix XVII.

17.5.4 Transmision of results of baseline assessment

Collection of further samples depends of the involvement at baseline. Dr. F. Bertoni therefore will communicate the results of the baseline investigation of each patient within 8 weeks from sending the samples to the SAKK Trials Office. The Trial Coordinator will immediately inform the investigator.

17.6 New molecular biology research questions

Any research question not included in the protocol has to be formulated in an amendment. This amendment has to consider the funding of the research and must be submitted to the SAKK Scientific Committee and the respective ethics committees for approval.

18 IMMUNOPHENOTYPING

18.1 Introduction

Infusion of rituximab results in a rapid and selective depletion of B lymphocytes. This has been documented in patients treated with rituximab for B lymphoproliferative malignancies or autoimmune disorders. Peripheral blood B lymphocyte depletion occurs within days, and studies in primates have shown that up to 70% of B lymphocytes in lymphoid organs are also rapidly cleared. Depending on the dose and the patient B lymphocytes may be undetectable for months, but a gradual recovery is normally observed 6 to 8 months after the final infusion. Although moderate and transient decreases in serum immunoglobulin levels have also been observed, B lymphocyte depletion by rituximab does not appear to be associated with an increased risk of major, opportunistic infection (14). However, as in patients with lymphoma and autoimmune disease, rituximab therapy routinely consists of a limited number of infusions, and studies reporting the effects of prolonged rituximab maintenance on lymphocyte subpopulations (e.g., B lymphocytes) and immunologic competence are scant. In addition, it has not yet been analyzed whether the relative degree of B lymphocyte depletion induced by rituximab maintenance correlates with clinical response or, vice versa, whether relapse/progression is paralleled or preceeded by B lymphocyte return.

18.2 Objectives

- assess evolution of cellular immunologic competence
- monitoring of B lymphocyte depletion and recovering
- correlation with infections

18.3 Endpoints

- Cellular immunologic competence: absolute counts of peripheral blood lymphocyte subpopulations ($CD19^+$ B lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes and $CD3^-$, $CD16/56^+$ NK cells) before and after induction treatment with rituximab, at 6 and 12 months since randomization during maintenance, and every 6 months thereafter until relapse/progression (up to 10 years from randomization).
- Period of peripheral blood B lymphocyte depletion (defined as $<0.005 \times 10^9$/l).

18.4 Methods

Percentages and absolute numbers of $CD19^+$ B lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes and $CD3^-$, $CD16/56^+$ NK cells will be determined by standard direct four-color staining and lyse/no-wash techniques on whole blood in conjunction with CD45/SSC gating for lymphocytes using a FACSCalibur flow cytometer and CellQuest^{PRO}/MultiSET software. The use of internal reference beads will allow for direct flow cytometric assessment of absolute numbers of lymphocyte subpopulations.

Only patients registered at Swiss centers will be included into this project. All patients that provide informed consent for laboratory subprojects should participate in this subproject.

18.5 Sampling

18.5.1 Sampling time points

3-4 ml peripheral blood in K_2EDTA tubes (spray-dried; do not use tubes with liquid EDTA) will be collected at the following time points:

- Within 21 days before registration
- At restaging (after induction therapy)
- At 6 months since randomization
- At 12 months since randomization
- Thereafter: every 6 months until relapse/progression (up to 10 years)

18.5.2 Samples handling

- After sample collection, the tube should be inverted immediately several times to ensure anticoagulation. No further handling (e.g., centrifugation) is required. Samples should be stored at room temperature at all times.
- A local research nurse or a data manager must be responsible for collection and shiping of blood samples.
- Appropriate sample tubes (K_2EDTA) may be obtained from the laboratory indicated below (section 18.5.3).

18.5.3 Sample shipping

Each sample of each individual patient should be send immediately after collection. The tubes must be clearly labeled (SAKK 35/03; unique patient number; date and time of sample collection) and shipped by EXPRESS (overnight express or courier) at ROOM TEMPERATURE to the following address:

FACS-Labor
Zentrum für Labormedizin
Kantonsspital Aarau
CH-5001 Aarau

Tel: 062 838 5320 (Monday to Friday 8:00 a.m. to 5:00 p.m.)
Tel: 062 838 5310 (Monday to Friday 5:00 p.m. to 8:00 a.m.; Saturday and Sunday)
E-mail: ingmar.heijnen@ksa.ch

The cover letter provided in appendix XVIII should accompany each sample.

Special envelopes with address stickers can be provided upon request. Samples should arrive at the above indicated address within 24 hours after sample collection. To avoid arrival of samples on Saturday, Sunday and national holidays (see section 7.1) samples should not be collected on Friday, Saturday, and on the day before national holidays. In case the above mentioned criteria are met, it is not necessary to contact the laboratory before shipment of a sample. However, in case of any doubt the indicated telephone numbers may be used.

The analysis will not be charged to the patient.

19 ECONOMIC EVALUATION

19.1 Rationale

Long-term treatment with rituximab up to 5 years is expensive, but may be of major benefit to the patient by significantly prolonging event-free survival. Therefore a comparison of incurred costs with achieved benefit in the form of increased event-free survival by way of an *incremental cost-effectiveness analysis* is highly justified.

For this trial, part of the trial medication will be provided free of charge by Roche. For the economic evaluation the costs will be estimated as if the medication had to be paid by the patient or his health insurance.

Costs of treatments will be very different between countries. It is anticipated that about 50% of all patients will be recruited in Switzerland, while the rest will come from several European and non-European countries. The costs would not be comparable between countries due to major differences between health care systems and real costs. Therefore, this economic evaluation is restricted to patients accrued in Switzerland.

19.2 Perspective

The economic evaluation study will be designed to adopt a restricted societal viewpoint. This means that all substantial direct costs to society incurred in treatment of the patient are to be evaluated. Indirect costs such as income loss due to the illness, treatment etc are not taken into account.

19.3 Methods

The comprehensive assessment of all costs related to the treatment and its intended and unintended effects is a very complicated and extensive task. Therefore, ways of performing a lean yet fairly accurate estimation of costs are sought.

Preliminary experience from the ongoing cost assessment in SAKK 16/00 (amendment 1) has to be taken into account in the design of the current study. In SAKK 16/00 it was considered that there is no single comprehensive source to document resource use for a patient. Therefore, it was decided to gather information from three independent sources:

- medical records at the treating institutions
- charge summaries from the health insurance companies
- patient diaries on medical resource use

It was postulated that these sources would yield a high degree of overlap, which had to be evaluated together in order to count all interventions only once. For the first 6 patients the information provided by their health insurance companies was excellent. All patients participating in the economic evaluation gave their consent to use their health insurance records. Based on this observation, we decided to perform a pilot study for the current trial, and then to restrict data collection for all other patients to the source which will provide a sufficient amount of information for a reasonable complete estimation of resource use. A patient diary like the one in SAKK 16/00 will not be used here because it is anticipated that patients would not be willing to complete it on a regular basis for 5 years.

Major sources of costs in this trial will be

- diagnostic and staging procedures
- rituximab treatment
- ambulatory treatment of adverse events, independent of their etiology

- hospitalizations due to adverse events, independent of their etiology

Costs that, from our chosen perspective, are not relevant include lost income, travel costs to the treating institution or to the private practitioner in charge of the patient, OTC drugs. Costs from these or similar sources will not be taken into account.

19.4 Analytic Technique

For the cost analysis we will try to identify and measure resource use by primary data gathering and then perform a cost valuation (assign prices to the resources used).

Two sources of data will be used for the first 10 randomized patients (5 per arm) who consent to participate in the economic evaluation, in order to get a complete overview of all resources used:

- medical records at the treating institutions
- charge summaries from the health insurance companies

These sources will of course yield overlapping information, and care will be taken to avoid double-counting. The medical records will be used to check this assumption and to identify further resource use not included in the insurance bills.

The costs incurred in the induction period will not be taken into account since they are not relevant for the incremental cost-effectiveness analysis.

The charges paid by the health insurers will not be used directly for valuation purposes because the relationship between these charges and resource use is often heavily distorted by subsidies, fixed-cost billing arrangements and differences between charges attributable only to the type of cover (Allgemein / Halb-privat / Privat and different levels of voluntary excess). Hopefully, insurance bills will constitute a complete source of information about resource use, with the exception of trial treatment provided for free by the manufacturer and documented on the trial CRFs.

If the information gathered from the two sources mentioned above will match to a large degree (plus or minus 10% in costs), then medical records will not be abstracted for further patients and data collection will be restricted to insurance bills. This decision may however be revised upon further experience from SAKK 16/00.

19.5 Data collection

The following data from the treatment phase and the follow-up need to be standardized after extraction from the insurance bills and patient records:

- Outpatient visits to the oncologist and other specialists (number and types of visits)
- Medication
- Unscheduled visits to oncologist, other physicians or emergency room (number and type of visits)
- Nursing consultations (number of visits)
- Laboratory, radiology and other diagnostic tests (number and type)
- Additional treatment related to the malignant disease
- Medical devices, supplies and equipment used
- Hospital stay

The data will be gathered by specialized personnel from the SIAK Coordinating Center. It will

cover the period of 5 years from randomization, irrespective of treatment success, i.e. it will be continued even if new treatment is applied after failure of rituximab maintenance.

19.6 Valuation (pricing)

The assignment of costs for these items of resource use will be on the following basis:

- Visits to oncologist's offices: the number of services rendered in each visit will be multiplied by the charges for individual services according to either a single tariff (probably TarMed), or to a weighted average of cantonal tariffs.
- Laboratory, radiology and other diagnostic tests as well as medical devices, supplies and equipment used will be priced according to the Spitalleistungkatalog (SLK) for inpatients and either TarMed or cantonal tariffs for outpatients.
- Cost of the study medication although provided partly free of charge by Roche and cost of concomitant medication according to official tariffs.
- Cost of hospital stay according to resource use, including administration and hotel costs.

19.7 Evaluation

The result of the evaluation will be presented as a ratio of incremental cost to incremental effectiveness. This will be based on event-free survival and will be expressed as the cost per 'natural unit' of the relevant outcome measure, i.e. as the cost per additional year of event-free survival. The evaluation will be carried out only once the clinical outcomes of the trial have been analyzed.

The primary evaluation will be the incremental cost-effectiveness ratio, expressed as average costs per gained year of event-free survival. This will be based on costs incurred up to the first event and on the time from randomization to this first event.

For patients relapsing within 5 years, the costs of the new treatment regimen after relapse will be estimated up to 5 years from randomization. The total costs incurred in 5 years will be put in relation to the event-free period under rituximab treatment. It will also be compared per se between the two treatment arms, since it is not foreseeable if the total costs will be higher under long-term maintenance or under observation, because the discontinuation of the rituximab maintenance may lead to earlier progression and to costs generated by a further line of chemotherapy. Such costs will also be estimated up to 5 years after randomization.

The comparison of costs arising in this trial with estimated costs for a standard therapy will be taken into consideration. This will depend on the availability of a reliable cost estimation from the literature.

Since the time horizon is 5 years in this trial, discounting the costs is advisable, and will be done by 2% or 3% per year. A sensitivity analysis using 0% and 5% discounting rates will be carried out as well.

The estimation of total costs of hospital stays is a difficult task due to the dualistic financing model used in Switzerland. However, an attempt will be undertaken to incorporate administrative and infrastructure costs into the analysis. Assumptions that are inevitable will be tested in a sensitivity analysis.

Further sensitivity analyses will be carried out to test for the robustness of results with regard to the tariffs and tax point values used in the evaluation as well as to the negligence of indirect costs.

19.8 Cooperation of the patient

The consent of the patient has already been incorporated into the template form provided in appendix IV of the protocol. In addition, the patient will be asked to sign a separate form entitling the health insurance company to disclose all bills and reimbursements to coworkers of SAKK (appendix V). The patient's refusal to participate in the economic evaluation will not be an exclusion criterion for the clinical trial.

20 ETHICAL CONSIDERATIONS

The protocol has been written and the trial is to be performed in accordance with the Declaration of Helsinki (15), the Guidelines for Good Clinical Practice issued by ICH (16) and requirements of regulatory authorities (for Switzerland 17).

Before entering any patients into this trial the investigator has to make sure that the trial has been approved by the local ethics committee and the center is opened by the national regulatory authorities.

Informed consent shall be obtained on a written form approved by the local ethics committee and signed by the patient and by the treating physician. Two copies of the informed consent sheet have to be signed, one of which will be handed to the patient.

The informed consent procedure must conform to the ICH guidelines for Good Clinical Practice. All patients will be informed of the aims of the trial, the possible adverse experiences, the procedures and possible hazards to which they will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but their medical records may be reviewed for trial purposes by authorized individuals other than their treating physicians.

An investigator must provide the patient or the representative with sufficient opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence. The information provided shall be in language understandable to the patient or the representative and may not include any content that appears to waive any of the patient's legal rights, or appears to release the investigator, the sponsor, or the institution from liability for negligence.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he / she wants. This will not prejudice the patient's subsequent care.

In case new data becomes available that shift risk / benefit ratio, the patient should be reconsented.

20.1 Premature withdrawal

Patients have the right to refuse further treatment for any reason and at any time. Patients who decide to withdraw from the trial should be asked whether they also want to withdraw their consent for their data to be used for the follow-up assessments. For the patient's security, a last examination should be performed.

Patients may be withdrawn at any time from trial treatment at the discretion of the investigator due to a serious adverse event or any other relevant medical condition. The patient will be transferred to the follow-up phase.

20.2 Treatment duration

In case a patient is in remission, the maximal treatment duration in the maintenance arm is defined to be 5 years. There are currently no data showing that longer durations may be beneficial.

21 ADMINISTRATIVE CONSIDERATIONS

The trial is to be performed in accordance with the declaration of Helsinki and the Guidelines of Good Clinical Practice (GCP).

21.1 Auditing

Regulatory authorities have the right to perform inspections. SAKK has the right to perform on site auditing upon reasonable prior notice during working hours.

21.2 Insurance

21.2.1 Swiss centers

The trial can be activated only in centers where the hospital has it's own insurance policy for clinical trials. Every patient has to be reported for coverage in this insurance. This insurance must remain in force until the study ends for the relevant patients. As soon as the future SIAK patient insurance is active, an amendment for Swiss centers will be issued to this effect, and subsequent patients will be covered by the SIAK patient insurance.

21.2.2 Foreign centers

The SAKK acknowledges the responsibility of the sponsor to provide adequate insurance coverage for patients included into the trial. Therefore, SAKK will contract insurance policies satisfying the national requirements for each participating center.

21.3 Monitoring

Source data must be available for auditing and monitoring.

21.3.1 Monitoring strategy

The monitor will contact and visit the investigators regularly. He / she will be allowed to inspect the various records of the trial in accordance with local requirements.

For this trial the expected average monitoring visit frequency is at least every 3 months during the treatment phase. That frequency may be adjusted based on the recruitment and the stage of the trial.

Before enrollment of the first subject or shortly after, a trial initiation visit should take place. The objective of this visit is to meet the local staff involved in the conduct of the trial (including sub-investigators, research nurse, data manager, pharmacist), to describe the main features of the protocol, the use of the case report forms (CRF), the practicalities of the trial and to distribute the trial specific trial master file (TMF). The initiation visit has to be documented on the 'checklist for initiation visit'.

During monitoring visits 100% Source Data Verification (SDV) will be performed for the first patient at a center for all data.

If no major variations are found, source data verification may be reduced (in accordance with the SAKK Trials Office) and only the following data will be reviewed for every patient:

- Informed consent
- Inclusion / exclusion criteria
- Primary endpoint (event-free survival)
- Serious Adverse Drug Reactions (SADR)

- Drug inventory log

In case of queries or inadequate data quality 100% SDV will be performed for further patients until acceptable data quality is obtained.

The monitors must provide copies of all monitoring reports to the Head of Trial Coordination at the SAKK Trials Office within 14 days and keep those reports accessible for other involved persons.

21.4 Quality assurance

Several procedures guarantee quality of trial conduct:

- Reviews of protocol and forms according to standard operating procedures (see. appendix I.)
- Data in case report forms will be entered into the database at the SAKK Trials Office. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistency.
- Data review by the trial chair or a delegated person (all case report forms will be reviewed and checked on medical content)
- Internal audit of the trial at the SAKK Trials Office at the SIAK Coordinating Center
- Safety monitoring
- Validation of database and statistical analysis
- Requirements for principal investigators for participation: signed and dated CV, principal investigator's agreement
- The trial will be monitored (SDV, verification of informed consent etc.)
- Validation of laboratory methods
- An authorization list must be kept at the center (see appendix XV)

21.4.1 Trial master file

A suggested table of contents for the trial master file can be found in appendix VII. All trial related correspondence should be filed in the trial master file.

21.5 Independent data monitoring committee (IDMC)

A group of independent experts will form a Data Monitoring Committee that will be responsible for monitoring the data of the clinical trial and the safety of the patients. This review will continue until the last patient has finished the treatment period. This group consists of independent experts not involved in this trial including at least 1 statistician and 2 tumor specialists. Further representatives from the SAKK may also participate in the meetings as invited guests.

The committee will be elected by the SAKK Executive Committee. This committee will provide recommendations concerning the progress of the trial and the safety of the patients after each meeting. Decisions are taken by the SAKK Scientific Committee using these recommendations.

Interim results of primary and secondary endpoints will not be disclosed to investigators but will be presented to the IDMC.

21.6 Modification of the protocol

21.6.1 Scientific amendment

Any amendment, which may impact on the conduct of the trial, potential benefit of the trial, or may affect patient safety, including changes of trial objectives, trial design, patient population, sample sizes, trial procedures, or significant administrative aspects, must have been accepted by the Scientific Committee. Such an amendment is termed scientific amendment and must have

the approval of the respective ethics committee and national authority (Swissmedic) prior to implementation.

21.6.2 Safety amendment

A safety amendment is a special kind of scientific amendment, which is released when it is necessary to eliminate immediate hazards to trial participants. A safety amendment requires immediate implementation at local sites, before approval of local ethics committee and Swissmedic (national authority) has been given.

21.6.3 Administrative amendment

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the trial is to be conducted. These administrative changes will be agreed upon by the trial chairperson and the SAKK Trials Office at the SIAK Coordinating Center, and will be documented in an administrative amendment. The local ethics committee may be notified of administrative changes at the discretion of the investigator.

21.7 Trial activation procedure

Investigators have to return to the SAKK Trials Office:

- The signed and dated Principal Investigator's Agreement, indicating that they will fully comply with the protocol and include an estimation of their yearly accrual (see appendix II)
- Signed and dated CV of the principal investigator
- The list of normal ranges, in their own institutions, of all laboratory data required by the protocol
- Ethics approval for his / her site, i.e a positive statement on the "Formular für die Beschlussmitteilung der Ethikkommission / Formulaire d'avis de la Commission d'éthique de la recherche" for Swiss centers.
- Approved patient information and informed consent. Any previous version submitted to the ethics committee (if any).
- A copy of the "Basisformular zur Einreichung eines biomedizinischen Forschungsprojektes / Formulaire de base pour la soumission d'un projet de recherche biomédicale" that has been submitted to the local ethics committee (for Swiss centers only).

Copies of **all** documents submitted to the ethics committee. Please refer to the "Basisformular zur Einreichung eines biomedizinischen Forschungsprojektes".

Once all these documents of a site are submitted to the SIAK CC, they will be forwarded to Swissmedic.

Swiss investigators will only be allowed to register patients in the trial after Swissmedic has opened the center. Foreign investigators will only be allowed to register patients after all national regulatory requirements are fulfilled.

21.8 Record retention

The investigator will retain copies of the patient's on trial documentation (CRFs, patient informed consent statement, laboratory printouts, drug transportation and return forms, and all other information collected during the trial) until at least 10 years after the termination of the trial (e.g. date of last visit of last patient receiving trial treatment).

In the event that the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer should be given in writing to SAKK.

21.9 Participation of foreign centers

Terms of Cooperation are available for collaborators outside of Switzerland. They will be provided to centers in a separate document.

22 PUBLICATION

The results of the trial will be published according to the SAKK publication guidelines.

Authors of the manuscript will include the Trial Chair(s) and leading investigators of the major participating groups, and investigators who have included more than 10% of the patients in the trial.

In case of participation of a foreign Cooperative Group in this SAKK trial, the contribution of the Cooperative Group has to be acknowledged according to its participation. Individual authors should be identified by the Cooperative Group. The individuals to be considered for authorship will be chosen by the Board of the corresponding Cooperative Group.

Manuscripts have to be presented to the Representative of the Cooperative Group prior to publication. He is responsible for distributing the manuscript within the foreign Cooperative Group. The Representative should give feedback to the SAKK Trial Chair and the SAKK Executive Committee.

In countries where individual centers participate, at least one author should have the opportunity to be included in the main publication(s), depending on the accrual and scientific input.

In all cases where journal policies permit, all investigators who contributed patients to the trial and further contributing persons will be acknowledged in an appendix.

None of the rules contained in these principles of publication should be allowed to contravene the principles that: all individuals who have made substantial intellectual, scientific and practical contributions to the trial and the manuscript should, where possible, be credited as authors; all individuals credited as authors should deserve that designation. It is the responsibility of the SAKK Executive Committee and the Trial Chair to ensure that these principles are upheld.

23 CONFIDENTIALITY

23.1 Copyright

The information contained in this protocol is copyright protected by the SAKK (Swiss Group for Clinical Cancer Research). This information is given for the needs of the trial and must not be disclosed to persons outside of SAKK without prior written consent of the SAKK Executive Committee.

For trial insurance related purposes, the protocol may be handed confidentially to an insurance company without prior notice to the SAKK.

Patients are allowed to see the protocol under confidentiality agreement.

23.2 Confidentiality

The name of the patients will not be disclosed to the SAKK Trials Office at the SIAK Coordinating

Center. A sequential unique patient number (UPN) will be attributed to each patient registered in the trial.

Identification of patients must be guaranteed at the center. In order to avoid identification errors, patient initials – two letters for the last name and one letter for the first name – and date of birth have to be provided on each form. Use the patient enrollment log. Patient confidentiality will be maintained according to applicable legislation. Patient must be informed of, and agree to, data and material transfer and handling, in accordance with the Swiss data protection law or local laws at least as stringent as the Swiss data protection law.

All information concerning rituximab supplied by Roche in connection with this trial and not previously published is considered confidential and proprietary information.

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25 APPENDICES

25.1 Appendix I: Protocol Sign-off Page

SAKK 35/03
Comparing two schedules of rituximab maintenance
in rituximab-responding patients with untreated, chemotherapy resistant
or relapsed follicular lymphoma:
A randomized phase III trial

The protocol SAKK 35/03 has been accepted by the Scientific Committee on November 20th 2002 and has passed the recommended review process for SAKK trials.
The final protocol is dated November 21st 2003.

SAKK Representative:

Name:..... Title: .....

Date:..... Signature:.....

Trial Chairperson:

Name:..... Title: .....

Date:..... Signature:.....

Trial Statistician:

Name:..... Title: .....

Date:..... Signature:.....

25.2 Appendix II: Principal investigator's agreement

SAKK 35/03. Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma:

A randomized phase III trial

I have thoroughly read the trial protocol SAKK 35/03.

Having read and understood the requirements and conditions of the trial protocol, I agree to conduct the trial as specified in the protocol. I agree to perform the clinical trial according to the international good clinical practice principles (ICH-GCP), the Declaration of Helsinki and according to national regulations (in Switzerland Vklin).

* I agree to ask for approval from the relevant Ethics Committee (EC) for the protocol, patient information and any amendment which needs approval. For administrative amendments not requiring a formal approval, I will obtain a letter of receipt from the EC. I will inform the SIAK CC in case the EC withdraws approval of the trial.

I only will accrue patients into this trial once the national authorities (in Switzerland Swissmedic) have opened the center. I further take notice that an amendment may only be applied once the national authorities have approved the amendment (except for safety or administrative amendments).

* I will attempt to complete the planned enrollment of _____ patients per year.

I agree to use the trial material, including rituximab, only as specified in the protocol.

I agree to appropriately inform patients on the trial including risks and means how to reduce/treat side effects. Informed consent will be obtained and signed from each patient prior to registration.

I understand that changes to the protocol must be made in form of an amendment that has obtained written approval of the SAKK Scientific Committee.

I understand that any violation of the protocol may lead to early termination of the trial at my institution.

I agree to report to the SAKK and the relevant EC, within one working day, any clinical adverse event that is serious (SAE), whether considered treatment-related or not. Follow-up reports will be provided within the timelines specified on the SAE Form.

I agree to keep accurate records on all patient information (case report forms and patient informed consent statement), and all other information collected during the trial for a minimum period of 10 years after termination of the trial.

I agree not to publish all or any part of the results of the trial carried out under this protocol, without the prior written consent of SAKK.

I will provide the required documents and information for monitors and all people responsible for auditing/inspecting.

I confirm to be present at the center and responsible for the whole trial period.
In case I leave the center, I will take care to hand over the responsibility of the principal investigators at the center to somebody else and I will inform the SAKK and the EC accordingly.

I agree not to close the trial at my center without prior written information of the SAKK.

* I agree to adequately train sub-investigators, data managers and further persons involved in the conduct of the trial.

* I agree to keep a list in the trial master file of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

I will take care that all members of the local trial team will convey with this agreement.

Principal investigator

Center: _____

Name: _____ Title: _____

Date: _____ Signature: _____

The signed original of this agreement has to be sent to the SIAK Coordinating Center. A copy of this page has to be submitted to your local EC and another has to be stored in your trial master file.

Note: Items with an asterisk (*) may not be applicable in case the principal investigator is located at a subcenter or is a private oncologist and communication with EC is effected via a main center.

25.3 Appendix III: List of participating centers/investigators

Institution	Investigator	email	Patients consented per year for Induction	PI: Principal Investigator SI: Sub-Investigator
Aargau: KSA KSB	 W. Mingrone C. Caspar	 walter.mingrone@ksa.ch clemens.caspar@ksb.ch	**4**	 PI PI
Basel: KSB Liestal	 R. Herrmann A. Lohri	 rherrmann@uhbs.ch andreas.lohri@ksli.ch	**4**	 PI PI
Bern: Inselspital	D. Betticher	daniel.betticher@insel.ch	**4**	PI
Graubünden: Chur	F. Egli	fritz.egli@ksc.gr.ch	**2**	PI
St. Gallen: KSSG	Th. Cerny F. Hitz	thomas.cerny@kssg.ch felicitas.hitz@kssg.ch	**8**	PI SI
Ticino: IOSI	M. Ghielmini	mghielmini@ticino.com	**8**	PI
Vaud: CHUV	N. Ketterer G. Canellini	nicolas.ketterer@chuv.hospvd.ch giorgia.canellini@chuv.hospvd.ch	**3**	PI SI
Zürich: USZ Triemli	 Ch. Taverna L. Widmer	 christian.taverna@usz.ch lucas.widmer@triemli.stzh.ch	**8** **3-4**	 PI PI
Italy: Milano (EIO)	G. Martinelli	giovanni.martinelli@ieo.it	**> 10**	PI
Serbia: Belgrad	B. Mihaljevic	bimih@Eunet.yu	**8**	PI
South Africa, Johannesburg	D.A. Vorobiof	voro@global.co.za	**10**	PI
Expected total accrual per year			**70-80**	

25.4 Appendix IV: Patient Information and Informed Consent

This template (Word file) can be downloaded from our website www.siak.ch (members section).

Patienteninformation

Version 1, 21. November 2003

VERGLEICH VON ZWEI ERHALTUNGSTHERAPIE-SCHEMATA MIT RITUXIMAB BEI PATIENTEN MIT EINEM UNBEHANDELTEN FOLLIKULÄREN LYMPHOM ODER NACH EINEM RÜCKFALL

Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK)
Studie 35/03

Sehr geehrte Dame
Sehr geehrter Herr

Ihr Arzt/Ihre Ärztin hat Ihnen mitgeteilt, dass Sie an einem bösartigen Tumor des lymphatischen Systems, einem sogenannten Non-Hodgkin-Lymphom vom follikulären Typ leiden. Lymphdrüsen-Krebs sprechen auf eine zytostatische Therapie (Chemotherapie) gut an, und eine Verkleinerung des Tumors bis zum Verschwinden wird in der Mehrzahl der Fälle beobachtet. Nach einer gewissen Zeit, die von Patient zu Patient verschieden lang ist, kommt es aber leider häufig zu einem Rückfall. Dieser kann wiederum mittels Chemo- oder Antikörper-Therapie behandelt werden.

Man hat Ihnen soeben vorgeschlagen, an der obgenannten Studie teilzunehmen. In dieser werden unterschiedliche Anwendungen eines antitumoralen Medikaments – Rituximab (Markenname Mabthera®) – geprüft. Dieses Medikament gehört nicht zur Medikamenten-Gruppe der Zytostatika. Es ist ein monoklonaler Antikörper, der mittels Gentechnologie hergestellt wird. Der Antikörper Rituximab ist gegen ein Eiweiss an der Oberfläche der bösartigen Lymphom-Zellen gerichtet. Der Antikörper erkennt die bösartigen Zellen und kann Mechanismen des Immunsystems aktivieren, die zur Abtötung der bösartigen Zellen führen. Diese Antikörper-Therapie zeigte bei einer beträchtlichen Anzahl Patienten eine gute Wirksamkeit.

Die übliche Therapie wird 4x in wöchentlichen Abständen durchgeführt. Eine kürzlich abgeschlossene Studie hat nun gezeigt, dass eine Erhaltungstherapie mit Rituximab während 8 Monaten (anschliessend an die sogenannte Induktionstherapie während 4 Wochen) eine Verlängerung der beschwerdefreien Zeit für die Patienten bringt.

Mit diesem Informationsblatt möchten wir Sie nun über eine klinische Studie informieren, an der Sie sich beteiligen können. Diese Studie wird von der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) durchgeführt.

Beschreibung und Ziele der Studie

Es soll geprüft werden, ob eine Verlängerung dieser Erhaltungstherapie mit Rituximab einen weiteren Vorteil für die Patienten bringt, d.h. das Intervall bis zu einem möglichen Rückfall verlängert. Um diese Frage beantworten zu können, erhält die Hälfte der Patienten die bisherige Standardtherapie (= 4malige Infusion in wöchentlichen Abständen während der Induktionsphase und eine 8-monatige Erhaltungstherapie von weiteren 4 Infusionen alle 2 Monate).

Bei der anderen Hälfte der Patienten wird die Erhaltungstherapie mit einer Infusion alle 2 Monate bis max. 5 Jahre oder bis zu einem allfälligen Rückfall weitergeführt. Es wird nach dem

Zufallsprinzip (Randomisation) entschieden, ob Sie Rituximab während 8 Monaten erhalten oder bis maximal für 5 Jahre.

Dabei werden nur jene Patienten für die Randomisation ausgewählt, bei denen die Erkrankung auf die Induktionstherapie angesprochen hat, d.h. einen Nutzen gezeigt hat.

Die Nachbeobachtungszeit für alle Patienten dauert bis 10 Jahre nach der Randomisation. Falls Sie einen Rückfall erleiden, sind jedoch keine weiteren Untersuchungen im Rahmen dieser Studie nötig.

Auswahl der Studienteilnehmer/Innen

Sie wurden für die Teilnahme an dieser Studie ausgewählt, weil Sie an einem follikulären Lymphom leiden. In dieser Studie sollen 270 Patienten behandelt werden, davon 135 in der Schweiz. Es ist geplant, dass während 3 Jahren Patienten in die Studie aufgenommen werden.

Vor Beginn der Behandlung wird Ihr Arzt/Ihre Ärztin beurteilen, ob Sie innerhalb dieser Studie behandelt werden können. Aus diesem Grunde müssen Sie eine ausführliche medizinische Untersuchung durchlaufen, welche eine Ultraschall-Untersuchung des Herzens und ein Echokardiogramm, eine Schichtröntgenaufnahme (Computertomogramm) zur Beurteilung der Tumorgrösse, eine Knochenmarks-Punktion sowie Blutentnahmen einschliesst. Je nach befallenen Organen müssen allenfalls weitere bildgebende Untersuchungen eingesetzt werden. All diese Untersuchungen werden im Zusammenhang mit einer Tumortherapie auch unabhängig von Ihrer Teilnahme an dieser Studie durchgeführt.

Mit Ihrem Einverständnis wird Sie Ihr Arzt/Ihre Ärztin beim Koordinationszentrum der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) in Bern für diese Studie registrieren.

Ablauf der Studie und Untersuchungen

Der monoklonale Antikörper Rituximab wird als Infusion in eine Vene verabreicht. Die Infusion dauert jeweils 3 bis 5 Stunden.

Zur Beurteilung Ihres Befindens und der Verträglichkeit der Behandlung sind während der Induktions- und Erhaltungstherapie Kontrolltermine bei Ihrem behandelnden Arzt /Ihrer behandelnden Ärztin notwendig, d.h. Sie werden vor jeder Infusion untersucht. Alle 6 Monate wird der Verlauf Ihrer Krankheit mittels einer Computertomografie beurteilt. Falls das Knochenmark auch durch den Lymphdrüsen-Krebs befallen war, sind auch weitere Knochenmarksuntersuchungen notwendig (12 Wochen und 15 Monate nach Therapiebeginn sowie jährlich für maximal 10 Jahre oder bis zu einem allfälligen Rückfall). Zusätzlich sind regelmässige Blutkontrollen notwendig. Dies sind die üblichen Untersuchungen bei einer Lymphomerkrankung. Die Nachbeobachtungs-Zeit beträgt maximal 10 Jahre nach der Randomisation.

Falls die Erkrankung während der Rituximab-Therapie voranschreitet, wird diese Therapie abgebrochen und Ihr Arzt/Ihre Ärztin wird mit Ihnen andere Behandlungsmöglichkeiten besprechen. Die Behandlung mit der Studienmedikation kann auch abgebrochen werden, wenn schwere Nebenwirkungen auftreten.

Risiken und Nebenwirkungen der Behandlung

Das innerhalb dieser Studie verwendete Medikament kann einige der nachfolgend genannten Nebenwirkungen verursachen. Zusätzlich besteht die Möglichkeit, dass sehr seltene schwerwiegende oder vorher unbekannte Nebenwirkungen auftreten.

Die häufigsten Nebenwirkungen von Rituximab sind: Fieber, Frösteln, Schüttelfrost, Hautausschläge, Übelkeit, Müdigkeit, Kopfschmerzen, „laufende“ Nase, Erbrechen. Die Nebenwirkung treten am häufigsten bei der ersten Verabreichung auf, weshalb Sie bei dieser Infusion streng überwacht werden. Selten können ein Blutdruckabfall oder Atembeschwerden auftreten. Falls dies eintritt, werden Sie über Nacht hospitalisiert, damit Sie weiter überwacht und entsprechend behandelt werden können.

Während den folgenden Verabreichungen werden solche Nebenwirkungen viel seltener beobachtet.

Forschung mit Knochenmark und Blutproben (nur für Patienten an Schweizer Zentren)

Mit Ihrem Einverständnis werden zusätzliche Untersuchungen mit Blut und Knochenmark durchgeführt.

Dabei wird erstens getestet, ob und wie sich Blutzellen, die für die Infekt-Abwehr wichtig sind, unter der Rituximab-Therapie verändern. Hierzu werden Ihnen zu den folgenden Zeitpunkten Blutproben entnommen: vor Beginn der Therapie, 12 Wochen und 15 Monate nach Therapiebeginn sowie danach alle 6 Monate während maximal 10 Jahren oder bis zu einem allfälligen Rückfall. Diese Untersuchungen werden am Kantonsspital Aarau durchgeführt.

Zweitens wird untersucht, wie sich Zellen mit einem Defekt in den Chromosomen, der für die Lymphom-Erkrankung mitverantwortlich ist, unter der Rituximab-Therapie verhalten, falls dieser Defekt vor Beginn der Therapie nachgewiesen werden kann. Diese zytogenetischen Untersuchungen werden im Blut und im Knochenmark durchgeführt.

Hierzu werden Ihnen zu den folgenden Zeitpunkten Blutproben und Knochenmark entnommen: vor Beginn der Therapie, 12 Wochen und 15 Monate nach Therapiebeginn sowie jährlich während maximal 10 Jahre oder bis zu einem allfälligen Rückfall. Diese Untersuchungen werden am Spital in Bellinzona durchgeführt.

Ihre Teilnahme an diesen Untersuchungen ist freiwillig. Wenn Sie auf die Teilnahme verzichten, können Sie trotzdem an der klinischen Studie teilnehmen. Es werden Ihnen oder Ihrer Krankenkasse keine Kosten für diese Untersuchungen verrechnet.

Vorsichtsmassnahmen

Es ist nicht bekannt, ob die Rituximab-Verabreichung bei Schwangeren zu einer Schädigung des ungeborenen Kindes führen kann, deshalb dürfen Frauen während der Teilnahme an dieser Studie nicht schwanger sein oder werden. Deshalb wird bei Frauen im gebärfähigen Alter ein Schwangerschaftstest durchgeführt. Alle Frauen, die an dieser Studie teilnehmen, müssen entweder jenseits der Wechseljahre sein, einen chirurgischen Eingriff, der zur Sterilität führt, hinter sich haben (Entfernung der Gebärmutter, Unterbindung der Eileiter), oder sie müssen während der gesamten Dauer der Behandlung und 12 Monate darüber hinaus eine wirksame Methode zur Empfängnisverhütung anwenden. Sie können diese Möglichkeiten mit Ihrem Arzt/Ihrer Ärztin besprechen.

Es ist nicht bekannt, ob die Rituximab-Verabreichung zu einer Störung der Spermienbildung führen kann, deshalb muss eine Zeugung während und 12 Monate nach der Behandlung durch geeignete Verhütungsmassnahmen (Tragen eines Kondoms beim Geschlechtsverkehr) verhindert werden.

Nutzen und Vorteile der Behandlung

Der erwartete Nutzen liegt in der Verlängerung der symptomfreien Zeit. Es ist nicht bekannt, ob Sie durch die Teilnahme an dieser Studie einen persönlichen Nutzen haben werden. Ihre Teilnahme wird jedoch einen Beitrag zum besseren Verständnis der Behandlung dieser Erkrankung leisten.

Andere Therapiemöglichkeiten

Ihr Arzt/Ihre Ärztin wird mit Ihnen die Möglichkeit einer Behandlung ausserhalb dieser Studie besprechen.

Neue Informationen

Ihr Arzt/Ihre Ärztin wird Sie über alle neuen Erkenntnisse informieren, die den Nutzen oder die Sicherheit dieser Behandlung betreffen könnten und welche einen Einfluss auf Ihre Entscheidung, sich an dieser Studie zu beteiligen, haben könnten.

Pharmaökonomie (nur für Patienten an Schweizer Zentren)

Im Rahmen dieser Studie soll zusätzlich eine Evaluation der damit verbundenen Behandlungskosten durchgeführt werden. Sie sind frei zu entscheiden, ob Sie an dieser Erhebung teilnehmen oder nicht.
Wir bitten Sie, zum gegebenen Zeitpunkt (vor der Randomisation), die separate Patienteninformation zu lesen.

Vertraulichkeit

Während dieser Studie werden Ihre Daten in anonymisierter Form gesammelt. Dabei werden Ihre Initialen sowie Ihr Geburtsdatum verwendet, und es wird Ihnen eine spezielle Studiennummer zugeteilt.

Ihre Krankenakte wird vertraulich behandelt und im Spital für mindestens 10 Jahre aufbewahrt.

Im Falle Ihrer Teilnahme an dieser Studie und mit Ihrem Einverständnis werden Ihre anonymisierten Daten an das Koordinationszentrum der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) in Bern weitergeleitet, wo sie vertraulich und ausschliesslich im Rahmen der wissenschaftlichen Tätigkeit der SAKK behandelt werden.

Für die Qualitätskontrolle der Studie ist es erforderlich, dass Ihre Krankenakten von speziell ausgewählten Personen, wie Studienmonitoren und –auditoren, durchgesehen werden können. Dies sind Personen, die sicherstellen, dass die Qualität der gewonnenen Daten hoch ist, und dass die Studie ordnungsgemäss durchgeführt wird. Mitglieder von staatlichen Behörden (z.B. Schweiz. Heilmittelinstitut Swissmedic) und die zuständige Ethikkommission können ebenfalls Einblick in Ihre Krankengeschichte nehmen. Alle Personen, die in irgendeiner Weise Einblick in Ihre Krankengeschichte haben, unterstehen der Schweigepflicht.

Die Vertraulichkeit Ihrer Daten wird in jedem Fall gewahrt, und Ihre Identität wird in keiner Publikation genannt.

Mit Ihrem Einverständnis wird Ihr Hausarzt von Ihrer Studienteilnahme in Kenntnis gesetzt.

Behandlungskosten

Zentren in der Schweiz:

Für Patienten mit einem unbehandelten follikulären Lymphom wird Rituximab für alle Infusionen von der Firma Roche kostenlos zur Verfügung gestellt.

Für die Patienten nach einem Rückfall, welche die Rituximab-Erhaltungstherapie mehr als 4x, d.h. für 5 Jahre oder bis zu einem allfälligen Fortschreiten der Erkrankung erhalten, wird Rituximab ab der 5. Infusion von der Firma Roche gratis zur Verfügung gestellt. Alle anderen nötigen Medikamente sind von der Arzneimittelbehörde (Swissmedic) zugelassen und die Kosten werden von den Krankenkassen übernommen, ebenso wie alle Arztbesuche, Blutentnahmen und radiologischen Untersuchungen. Durch die Teilnahme an dieser Studie fallen Ihnen und Ihrer Krankenkasse keine zusätzlichen Kosten an.

Zentren im Ausland:

Der Text muss allenfalls vom Zentrum ergänzt werden.

Versicherung

Zentren in der Schweiz:

Der Text muss vom Zentrum ergänzt werden.

Zentren im Ausland:

Die SAKK (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung) ersetzt Ihnen Schäden, die Sie gegebenenfalls im Rahmen des klinischen Versuchs erleiden.

Zu diesem Zweck hat das SIAK (Schweizerisches Institut für Angewandte Krebsforschung) eine Versicherung bei der Gerling Allgemeine Versicherungsgesellschaft abgeschlossen.

Stellen Sie während oder nach dem klinischen Versuch gesundheitliche Probleme oder andere Schäden fest, so wenden Sie sich bitte an den verantwortlichen Arzt/die verantwortliche Ärztin (s. unten, "Kontaktperson"). Er/Sie weiss über die geltende Gesetzgebung Bescheid, verfügt über die entsprechenden schriftlichen Unterlagen und wird für Sie die notwendigen Schritte einleiten.

Rechte des Teilnehmers

Die Teilnahme an dieser Studie ist freiwillig. Sie können frei entscheiden, nicht an der Studie teilzunehmen oder Ihre Zustimmung zur Teilnahme an der Studie jederzeit zurückzuziehen, auch ohne Angabe von Gründen. Dies wird keinen Einfluss auf Ihre weitere Betreuung haben.

Falls Sie Ihre Zustimmung zur Teilnahme an der Studie zurückziehen, wird man Sie bitten, eine letzte Untersuchung vornehmen zu lassen. Damit soll sichergestellt werden, dass allenfalls vorhandene Beeinträchtigungen erkannt und behandelt werden können.

Falls Sie wünschen, dass Ihre Daten nicht mehr weitergeleitet werden oder ganz gelöscht werden sollen, bitten wir Sie, dies Ihrem behandelnden Arzt/Ihrer behandelnden Ärztin mitzuteilen.

Für die Teilnahme an der Studie erhalten Sie keine finanzielle Entschädigung.

Aufgaben des Teilnehmers

Bitte informieren Sie Ihren Arzt über jegliche Nebenwirkungen und Symptome. Es ist auch wichtig, dass Sie alle Medikamente nennen, welche Sie eventuell zusätzlich einnehmen.

Während der Teilnahme an der Studie und zwölf Monate darüber hinaus müssen Sie adäquate Verhütungsmethoden anwenden (siehe Absatz Vorsichtsmassnahmen).

Für die Zeit der Teilnahme an dieser Untersuchung dürfen Sie an keiner anderen klinischen Studie teilnehmen.

Unfreiwilliges Ausscheiden aus der Studie

Im Interesse Ihrer Gesundheit kann Ihr behandelnder Arzt/Ihre behandelnde Ärztin entscheiden, Sie in folgenden Fällen aus der Studie auszuschliessen: bei Auftreten schwerer Nebenwirkungen, einer schweren Krankheit oder bei Nebenwirkungen, welche die Verabreichung der Medikamente verunmöglichen. In solchen Fällen wird für Ihre Sicherheit bei Beendigung Ihrer Teilnahme eine klinische Untersuchung durchgeführt.

Ebenfalls kann die SAKK beim Bekanntwerden von neuen wissenschaftlichen Resultaten die Studie abbrechen. Ihre Weiterbehandlung, falls Sie dies wünschen, ist aber garantiert.

Ethische Beurteilung

Die vorliegende Studie wurde von der zuständigen Ethischen Kommission ..... [Ort] genehmigt. Datum der Genehmigung: .....

Die Studie wurde ebenfalls vom Forschungsrat der SAKK gutgeheissen und der zuständigen Behörde (Swissmedic/Schweizerisches Heilmittelinstitut) gemeldet.

Kontaktperson

Während oder nach dieser Studie können Sie alle Fragen oder Probleme mit der folgenden Kontaktperson besprechen:

Dr. med. Ch. Taverna

Klinik und Poliklinik für Onkologie, Universitätsspital Zürich

Rämistrasse 100, 8091 Zürich

Telefonnummer: 01 255 22 14

Einwilligungserklärung nach schriftlicher und mündlicher Aufklärung

Version 1, 21. November 2003

Eine multizentrische Phase III-Studie

Vergleich von zwei Erhaltungstherapie-Schemata mit Rituximab bei Patienten mit einem unbehandelten follikulären Lymphom oder nach einem Rückfall.

Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK)
Studie 35/03

Patient/in

Name: ..... Vorname(n): .....

Geburtsdatum: ..... Heimatort / Nationalität: .....

Wohnadresse: .....

Zur Zeit in Behandlung bei (Arzt / Klinik, Stempel):

Die vorliegende Erklärung betrifft die folgende Studie 35/03 der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK):

Der/die Unterzeichnende bestätigt die folgenden Punkte:

- Ich wurde über die Diagnose und die Behandlungsmöglichkeiten aufgeklärt.
- Ich wurde vom unterzeichnenden Arzt mündlich und schriftlich über die Gründe einer Teilnahme bei dieser Studie informiert. Dies beinhaltet auch die Ziele, das Vorgehen der festgelegten Behandlung, mögliche Vor- und Nachteile sowie eventuelle Risiken und den zu erwartenden Nutzen.
- Ich bestätige, dass ich eine Patienteninformation - datiert vom 21. November 2003 – und eine vom betreuenden Arzt unterschriebene Einverständniserklärung ausgehändigt bekommen habe.
- Ich habe die Patienteninformation zur Studie SAKK 35/03 gelesen und den Inhalt verstanden.
- Ich habe zur Kenntnis genommen, dass mir jedes neue Studienergebnis mitgeteilt wird, sofern dasselbe geeignet ist, meine Sicherheit als Studienteilnehmer zu beeinflussen. Im Interesse meiner Gesundheit kann mich mein behandelnder Arzt jederzeit von der Studie ausschliessen.
- Ich wurde informiert, dass eine Versicherung für die Teilnehmer an dieser Studie abgeschlossen wurde.
- Ich hatte ausreichend Gelegenheit, Fragen zu stellen. Meine Fragen wurden mir zufriedenstellend beantwortet.
- Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
- Ich nehme zur Kenntnis, dass mir das Recht zusteht, die Teilnahme zu verweigern oder eine einmal erteilte Zustimmung zu einem späteren Zeitpunkt zu widerrufen. Daraus ergeben sich keine Nachteile

für meine weitere medizinische Betreuung. In diesem Fall werde ich zu meiner Sicherheit abschliessend medizinisch untersucht.

- Ich wurde auf meine Rechte als Studienteilnehmer hingewiesen.

- **Ich erkläre mich bereit, freiwillig an der Studie SAKK 35/03 teilzunehmen.**
  Bei meiner Einwilligung wurde ich nicht von meinem behandelnden Arzt oder einem anderen Angehörigen des Spitals unter Druck gesetzt.
- Ich bin mir bewusst, dass während der Studie die in der Patienteninformation genannten Aufgaben einzuhalten sind.
- Ich verpflichte mich insbesondere, meinen behandelnden Arzt über allfällig auftretende Gesundheitsschädigungen, Nebenwirkungen und über zusätzliche Medikamente, die ich einnehme, zu informieren.
- Ich bin damit einverstanden, dass für die genaue Bestimmung der Blutzellen und für zytogenetische Untersuchungen Blutproben und Knochenmark an ein spezialisiertes Labor versandt werden**.**

  ☐ Einverstanden ☐ Nicht einverstanden

  Falls ich mit diesem Teil der Studie nicht einverstanden bin, kann ich trotzdem an der Behandlungsstudie teilnehmen. Die Untersuchungsresultate werden mir nicht mitgeteilt.
- Falls ich meine Zustimmung zu einem späteren Zeitpunkt widerrufe, dürfen meine bis dahin gesammelten Daten weiterverwendet werden.

  ☐ Einverstanden ☐ Nicht einverstanden

- Ich bin damit einverstanden, dass die erforderlichen Personendaten anonym an die zuständigen Stellen der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung zur Bearbeitung weitergeleitet und dort gespeichert beziehungsweise aufbewahrt werden.
  Dabei werden alle Vorkehrungen getroffen, um eine Offenlegung dieser Personendaten gegenüber unbefugten Dritten zu vermeiden.
- Ich bin damit einverstanden, dass die zuständigen, autorisierten Fachleute der SAKK, der Behörden und der Ethikkommissionen zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Die vorliegende Erklärung gilt bis auf Widerruf.

Ort	Datum	Unterschrift des Patienten
.....	.....	.....
Ort	Datum	Unterschrift des behandelnden Arztes
.....	.....	.....

Bemerkungen des behandelnden Arztes: .....

.....

25.5 Appendix V: Patient information and informed consent for pharmaeconomical part (for Swiss centers only)

SAKK 35/03

Vergleich von zwei Erhaltungstherapie-Schemata mit Rituximab bei Patienten mit einem unbehandelten follikulären Lymphom oder nach einem Rückfall.

Patienteninformation bezüglich Kostenerhebung

Die Kosten unseres Gesundheitswesens sowie die Kostenwirksamkeit medizinischer Behandlungen sind in letzter Zeit immer stärker ins Bewusstsein der Öffentlichkeit gelangt. Weder der therapeutische Nutzen der verlängerten Erhaltungstherapie mit Rituximab in der Behandlung von follikulären Lymphomen noch die dadurch verursachten Kosten können heute abgeschätzt werden. Um für zukünftige gesundheitspolitische Entscheide Grundlagen zur Beurteilung der Kostenwirksamkeit der verlängerten Erhaltungstherapie zu haben, wird eine Zusatzstudie zur Studie SAKK 35/03, an welcher Sie teilnehmen, durchgeführt. Wir bitten Sie, uns mit Ihrer Zusage zur Teilnahme an der Kostenerhebung zu unterstützen. Ihre Entscheidung, bei dieser Erhebung teilzunehmen oder nicht, hat aber keinen Einfluss auf die Teilnahme an der Hauptstudie oder auf die Behandlung, die Sie erhalten werden. Zusätzliche medizinische Behandlungen werden im Rahmen dieser Erhebung nicht nötig sein.

Wenn Sie mit der Teilnahme einverstanden sind, bitten wir Sie um Ihre Erlaubnis, Daten bezüglich der Kosten Ihrer Pflege aus den Aufzeichnungen aller Ärzte und Pflegepersonen zu erheben, welche während der Studienphase für Sie sorgen. Ebenfalls benötigen wir Ihre Erlaubnis, von Ihrer Krankenkasse Informationen zu erhalten. Alle Daten, die wir gewinnen, werden direkt ans Studien-Koordinationszentrum geleitet und dort mit strikter Vertraulichkeit behandelt. Es werden unter keinen Umständen irgendwelche Daten bezüglich Ihrer individuellen Behandlung an Drittpersonen weitergeleitet.

Die Kostenerhebung wird durchgeführt durch das Schweizerische Institut für Angewandte Krebsforschung (SIAK), Netzwerk für "Outcome Research", Effingerstrasse 40, 3008 Bern, Tel. 031 / 389 91 91, Fax. 031 / 389 92 00, E-mail: rudolf.maibach@sakk.ch, (Projektleiter Dr Rudolf Maibach).

Ihr Arzt wird allfällige weitere Fragen, die Sie zur ökonomischen Evaluation haben, beantworten.

Besten Dank für Ihr Interesse und Ihre Mitarbeit.

SAKK 35/03

Vergleich von zwei Erhaltungstherapie-Schemata mit Rituximab bei Patienten mit einem unbehandelten follikulären Lymphom oder nach einem Rückfall.

(for Swiss centers only **)**

Einverständniserklärung zur Teilnahme an der Kostenerhebung

Wir danken Ihnen, dass Sie der Teilnahme zur Kostenerhebung zugestimmt haben. Damit wir die nötigen Daten in den Aufzeichnungen Ihrer Ärzte und von anderen Pflegepersonen sowie von Ihrer Krankenkasse sammeln können, bitten wir Sie, diese Einverständniserklärung zu unterschreiben.

- Mein Arzt hat mir die Bedeutung dieser Zusatzstudie erklärt, und ich verstehe die Konsequenzen meines Einverständnisses zur Teilnahme.

Ich, der/die Unterzeichnende ..... __ __ /__ __19__ __

(Name, Vorname) (Geburtsdatum)

bin momentan in Behandlung bei Dr. .....

(Name des Arztes)

und nehme am Forschungsprojekt „Vergleich von zwei Erhaltungstherapie-Schemata mit Rituximab bei Patienten mit einem unbehandelten follikulären Lymphom oder nach einem Rückfall“ (SAKK 35/03) teil.

Ich gebe hiermit meine Erlaubnis an Projektmitarbeiter, studienbezogene Daten aus den Aufzeichnungen von allen Ärzten und anderen Pflegepersonen zu sammeln, die mich während einer 5-jährigen Periode betreuen, beginnend am …….....……...

(Datum der Randomisation)

Zudem gebe ich meine Erlaubnis für den/die Vertrauensarzt/ärztin meiner Krankenkasse

.....

.....

(Adresse der Krankenkasse)

die notwendigen Daten für diese Studie betreffend meiner Behandlung und Untersuchungen den Mitarbeitern der Kostenerhebung zur Verfügung zu stellen.

Persönliche, für die Studie gesammelte Daten werden nicht an Ihren behandelnden Arzt oder an Drittpersonen weitergegeben.

....

Unterschrift des Patienten Ort / Datum

DAS ORIGINAL DIESES DOKUMENTES WIRD BEI IHREM ARZT AUFBEWAHRT. SIE ERHALTEN EINE KOPIE.

SAKK 35/03

Vergleich von zwei Erhaltungstherapie-Schemata mit Rituximab bei Patienten mit einem unbehandelten follikulären Lymphom oder nach einem Rückfall.

(for Swiss centers only **)**

Gründe für eine Nichtteilnahme an der Kostenerhebung

Sehr geehrter Herr, sehr geehrte Dame

Ihr Arzt hat Sie über die Durchführung einer Kostenerhebung, verbunden mit der klinischen Studie, an welcher Sie teilnehmen, informiert. Sie haben sich entschlossen, nicht an dieser Kostenerhebung teilzunehmen, eine Entscheidung, welche wir natürlich respektieren. Trotzdem wäre es für uns sehr hilfreich, wenn Sie kurz Ihre Gründe dafür beschreiben würden, so dass wir einen Eindruck gewinnen können über die Bereitschaft gegenüber solchen Fragestellungen bei den Patienten.

Wir danken Ihnen für Ihre Mitarbeit.

Grund/Gründe für die Nichtteilnahme:

.....

.....

.....

.....

....

Initialen und Geburtsdatum des Patienten UPN

25.6 Appendix VI: Freigabe von Daten aus Krankenkassendossiers zu Forschungszwecken (for Swiss centers only)

An:

Den/die verantwortliche/n Vertrauensarzt/-ärztin der Krankenkasse:

.....

.....

.....

(Adresse der Krankenkasse)

Sehr geehrter Herr / Sehr geehrte Dame

Ich

……

(Name, Vorname)

Versicherungs-Nummer.....

nehme momentan an der Studie SAKK 35/03 teil, welche den Effekt von verlängerter Rituximab-Erhaltungstherapie untersucht. In Zusammenhang mit dieser Studie wird eine Kostenerhebung durchgeführt, welche die Kostenwirksamkeit der Erhaltungstherapie in dieser Krankheit erfassen will. Mit meiner Unterschrift gebe ich die Erlaubnis, Daten von meinen Versicherungsaufzeichnungen dem Studienpersonal am SIAK Koordinationszentrum in Bern freizugeben. Diese Daten werden mit strikter Vertraulichkeit behandelt. Sie werden unter keinen Umständen an Drittpersonen weitergegeben.

Die Studie wird in Zusammenarbeit mit meinem behandelnden Arzt/meiner Aerztin durchgeführt und durch das Schweizerische Institut für Angewandte Krebsforschung (SIAK) Netzwerk für "Outcomes Research" koordiniert.

SIAK Koordinationszentrum, Effingerstrasse 40, 3008 Bern, Tel. 031 / 389 91 91, Fax. 01 / 389 92 00, E-mail: rudolf.maibach@sakk.ch (Kontaktperson: Dr. Rudolf Maibach)

Falls Sie Fragen haben, kontaktieren Sie bitte Dr. Maibach.

Mit freundlichen Grüssen

....

Unterschrift des Patienten Ort / Datum

Beilage: Kopie der Einverständniserklärung für die Kostenerhebung

25.6.1 Freigabe von Daten aus Patientendossiers zu Forschungszwecken

An:
Pflegepersonal verantwortlich für die Pflege von Patienten in der Studie SAKK 35/03

Sehr geehrte Dame / Sehr geehrter Herr

Ich …….....……..….....

(Name, Vorname)

nehme momentan an der Studie SAKK 35/03 teil, welche den Effekt von verlängerter Rituximab-Erhaltungstherapie bei follikulären Lymphomen untersucht. In Zusammenhang mit dieser Studie wird eine Kostenerhebung durchgeführt, welche die Kosteneffektivität der verlängerten Erhaltungstherapie in dieser Krankheit feststellen will. Mit meiner Unterschrift gebe ich Ihnen die Erlaubnis, dem Personal am SIAK Koordinationszentrum Zutritt zu medizinischen Aufzeichnungen zu Forschungszwecken zu gewähren. Die extrahierten Daten werden mit strikter Vertraulichkeit behandelt und anonym aufbewahrt. Sie werden unter keinen Umständen an Drittpersonen weitergegeben.

Die Studie wird in Zusammenarbeit mit meinem Onkologen durchgeführt und durch das Schweizerische Institut für Angewandte Krebsforschung (SIAK), Netzwerk für "Outcomes Research" koordiniert.

SIAK Koordinationszentrum, Effingerstrasse 40, 3008 Bern, Tel. 031 / 389 91 91, Fax. 01 / 389 92 00, E-mail: rudolf.maibach@sakk.ch (Kontaktperson: Dr. Rudolf Maibach)

Falls Sie Fragen haben, kontaktieren Sie bitte Dr. Maibach.

Mit freundlichen Grüssen

....

Unterschrift Ort / Datum

Beilage: Kopie der Einverständniserklärung für die Kostenerhebung

25.7 Appendix VII: Table of Contents of Trial Master File

1. Protocol

- Final version
- Amendments (if any)

2. Responsibilities / Qualifications

- Authorization list
- Signed and dated principal investigator's agreement
- Signed and dated CV of principal investigator (not older than 2 years)
- Signed and dated CV of sub-investigator(s) (not older than 2 years)

3. CRFs

- Blank set of case report forms

4. Center documents

- Approval of regulatory authority
- Insurance statement

5. Ethics committee

- LREC/IRB letter of approval including correspondence
- Approved patient information and informed consent, locally adapted
- LREC members list
- Annual reports
- Documentation of SAE/SADR reported to the ethics committee

6. Patients

- Patient enrollment and identification list
- Copies of informed consents for enrolled patients

7. Laboratory

- Up-to-date laboratory reference ranges for hematology and biochemistry
- Copy of laboratory accreditation/certificate

8. Drug related forms

- Order fax for Mabthera® / Shipping records
- Drug inventory log for Mabthera®

9. Information on trial treatment

- Investigator's Drug Brochure (to be filed separately)
- Prescribing information
- Scientific publications

10. Safety relevant information

- SAKK Serious Adverse Event Form
- Documentation on SAEs occurred at center
- Safety information
- Safety alert letters

11. Monitoring

- Copy of monitors' checklist of initiation visit
- Monitoring visit log
- Follow-up letters of monitoring visits

12. Audits / Inspection

13. Clinical study report / Publications

14. Correspondence / Meeting notes

25.8 Appendix VIII: WHO Staging system

Follicular Cell Lymphomas: Grading and Variants

(Reference 11)

Grade 1	0-5 centroblasts/hpf
Grade 2	6-15 centroblasts/hpf
Grade 3	15 centroblasts/hpf
3a	15 centroblasts, but centrocytes are still present
3b	Centroblasts form solid sheets with no residual centrocytes

Variants

- Cutaneous follicle center lymphoma
- Diffuse follicle center lymphoma
  - Grade 1 0-5 CB/hpf
  - Grade 2 6-15 CB/hpf

25.9 Appendix IX: Response criteria

Criteria for Evaluation of Response in Non-Hodgkin's Lymphoma

Note: The following criteria are based on Cheson BD, et al, 1999 (1).

25.9.1 Complete Response (CR)

A complete response requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities definitely assignable to NHL
2. All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. Bone marrow, if positive at baseline, must be histologically negative for lymphoma.

25.9.2 Complete Response, unconfirmed (CRu)

CRu includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

- A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
- Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia)

25.9.3 Partial Response (PR)

A partial response requires the following:

- ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase in the size of the other nodes, liver, or spleen
- Splenic and hepatic nodules must regress by at least 50% in the SPD.
- With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
- No new sites of disease

25.9.4 Stable Disease (SD)

Stable disease is defined as less than a PR (as described above) but not progressive disease (see below).

25.9.5 Relapsed disease (after CR, CRu) requires the following:

- Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.
- ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

25.9.6 Progressive disease (after PR or SD)

Progressive Disease is defined as follows:

- ≥50% increase from nadir in the SPD of any previously identified abnormal node
- Appearance of any new lesion during or at the end of therapy

Criteria for Evaluation of Response in Non-Hodgkin's Lymphoma

Response Category	Physical Examination/ Evaluable lesions	Lymph Nodes	Lymph Node Masses	Bone Marrow	New sites
CR	Normal or Spleen regressed in size and not palpable (if enlarged before therapy) Liver and kidneys decreased in size (if enlarged before therapy)	Regressed to normal size, i.e. for **nodes > 1.5 cm** before therapy: ≤ 1.5 cm in their greatest transverse diameter (GTD) for **nodes between 1.1 to 1.5 cm** GTD: decreased to ≤ 1 cm or by more than 75% in the sum of the products of the greatest diameters (SPD)	Regressed to normal size, i.e. for **masses > 1.5 cm** before therapy: ≤ 1.5 cm in their greatest transverse diameter (GTD) for **masses between 1.1 to 1.5 cm** GTD: decreased to ≤ 1 cm or by more than 75% in the sum of the products of the greatest diameters (SPD)	Normal	No
CRu	See under CR	See under CR	A residual **lymph node mass > 1.5 cm** in GTD before therapy has regressed > 75% in the SPD. Individual lymph node that were previously confluent must have regressed by more than 75% in their SPD	Indeterminate	No
PR	No increase in size of liver or spleen decrease in intensity for PET (if done)	≥ 50 % decrease in SPD of the selected nodes No increase in the size of the other nodes Splenic and hepatic nodules must regress by at leas 50% in the SPD (if involved)	50% decrease in SPD of the selected nodal masses	Irrelevant	No
SD	Stable disease is defined as less than a PR (as described above) but not progressive disease (see below).				
Relapse (after CR or CRu)	Enlarging liver/spleen or increase in intensity for PET (if done)	≥50% increase in the size (GTD) of previously involved sites or ≥50% increase in greatest diameter of any previously identified node greater than 1.1 cm in its short axis	≥50% increase in the size (GTD) of previously involved sites or ≥50% increase in the SPD of more than one previously identified node.	Reappearance	Yes
Progression (after PR or SD)	Enlarging liver/spleen or increase in intensity for PET (if done)	≥50% increase from nadir in the SPD of any previously identified abnormal node	≥50% increase from nadir in the SPD of any previously identified abnormal site	Reappearance	Yes

25.10 Appendix X: WHO Performance Status

0 Fully active, able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

5 Dead

25.11 Appendix XI: Schedule of evaluations and investigations

An adaptable scheduler (Excel file) can be downloaded from our website www.siak.ch (members section) or will be provided on request.

Induction treatment: Arm A and B

Baseline evaluations		**Induction therapy**				**Restaging and randomization**
Week	-3-0	1	2	3	4	11-13
Month	-1					3
Informed consent	x					
for Swiss centers only Informed consent for economic evaluation						x
Inclusion/exclusion	x					x
Rituximab infusion		**x**	**x**	**x**	**x**	
Medical history	x					x
Physical examination (including performance status, PS)	x					x
Lab-hematology Hemoglobin, WBC, Thrombocytes, Neutrophils Monocytes, Lymphocytes	x					x
Lab-biochemistry Creatinine, bilirubin, ASAT or ALAT, alkaline phosphatase	x					x
Immunoglobulin IgA, IgM and IgG	x					x
LDH ESR CRP	x x x					x x
Bone marrow Aspirate and trephine at baseline	x[1)]					x[2)]
for Swiss centers only Bone marrow to Bellinzona	x					x[2)]
for Swiss centers only Blood to -Aarau -Bellinzona	 x x					 x x[2)]
Tumor staging CT scan of neck, thorax, abdomen and pelvis or MRI if CT cannot be performed	x					x
Echo or MUGA Cardiac ejection fraction	x	Upon clinical indication				
Pregnancy test If applicable	x					
Baseline symptoms/ Adverse events	Assess prior to/throughout treatment phase					

[1)] may be taken up to 3 months prior to registration

[2)] Repeat at restaging and later (only if involved at baseline)

Arm A – maintenance x4

Evaluations and procedures	**Maintenance phase**				**Follow-up phase for 10 years after randomization** **until relapse/progression**				**after relapse/PD**	
Months since randomization	0	2	4	6	9	12	Every 3 months thereafter	Every 6 months thereafter	Every 12 months thereafter	Every 12 months
Rituximab infusion	**x**	**x**	**x**	**x**						
Medical history	x	x	x	x	x	x	x			x[3)]
Physical examination (including PS)	x	x	x	x	x	x	x			x
Lab-hematology Hemoglobin, WBC, Thrombocytes, Neutrophils, Monocytes, Lymphocytes	x	x	x	x						
Lab-biochemistry Creatinine, bilirubin, ASAT or ALAT, alkaline phosphatase	Upon clinical indication									
Immunoglobulin IgA, IgM and IgG				x		x		x		
LDH	x	x	x	x	x	X		x		
Bone marrow Aspirate and trephine. Repeat only if involved at baseline						x[1) 2)]			x[1) 2)]	
for Swiss centers only Bone marrow to Bellinzona						x[1) 2)]			x[1) 2)]	
for Swiss centers only Blood to -Aarau -Bellinzona				x x[1)]		x x[1) 2)]		x	 x[1) 2)]	
Tumor staging CT scan of neck, thorax, abdomen and pelvis or MRI if CT cannot be performed				x		x		x		
Echo or MUGA Cardiac ejection fraction	upon clinical indication									
Adverse events	Record throughout treatment phase and up to 30 days after last medication administration. AE assessment visit should be fixed at 30 days after last administration. Late toxicities should be assessed in the follow up phase.									

[1)] Repeat only if involved at baseline

[2)] Repeat at relapse/progression

[3)] Document survival status, late toxicities and new therapies

Arm B – maintenance for 5 years or until relapse/progression, unacceptable toxicity or death whichever occurs first

Evaluations and procedures	**Maintenance phase for 5 years or until relapse/progression or unacceptable toxicity or death**										**Follow-up phase for 10 years after randomization**			
											<u>until</u> relapse/ progression			**<u>after</u> relapse/PD**
Month	0	2	4	6	8	10	12	Every 2 months thereafter	Every 6 months thereafter	Every 12 months thereafter	Every 3 months	Every 6 months	Every 12 months	Every 12 months
Rituximab infusion	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**						
Medical history	x	x	x	x	x	x	x	x			x			x[3)]
Physical examination (including PS)	x	x	x	x	x	x	x	x			x			x
Lab-hematology Hemoglobin, WBC, Thrombocytes, Neutrophils, Monocytes, Lymphocytes	x	x	x	x	x	x	x	x						
Lab-biochemistry Creatinine, bilirubin, ASAT or ALAT, alkaline phosphatase	Upon clinical indication													
Immunoglobulin IgA, IgM and IgG				x		x			x			x		
LDH	x	x	x	x			x		x			x		
Bone marrow Aspirate and trephine. Repeat only if involved at baseline							x[1)]			x[1) 2)]			x[1) 2)]	
for Swiss centers only Bone marrow to Bellinzona							x[1)]			x[1) 2)]			x[1) 2)]	
for Swiss centers only Blood to -Aarau -Bellinzona				x x[1)]			x x[1)]		x	x[1) 2)]		x	x[1) 2)]	
Tumor staging CT scan of neck, thorax, abdomen and pelvis or MRI if CT cannot be performed				x			x		x			x		
Echo or MUGA Cardiac ejection fraction	upon clinical indication													
Adverse events	Record throughout treatment phase and up to 30 days after last medication administration. AE assessment visit should be fixed at 30 days after last administration. Late toxicities should be assessed in the follow up phase.													

[1)] Repeat only if involved at baseline

[2)] Repeat at relapse/progression

[3)] Document survival status, late toxicities and new therapies

25.12 Appendix XII: Guidelines for the administration of rituximab

The following guidelines are recommendations, please consult also the official product information in your country.

Mode of administration: MABTHERA® (rituximab = IDEC-C2B8) is provided in 100 mg (10 ml) and 500 mg (50 ml) pharmaceutical grade vials at a concentration of 10 mg of protein/ml. Vials should be stored in the refrigerator at 2-8°C. Do not freeze or store at room temperature.

Dilution: The prescribed dose of rituximab should be diluted in NaCl 0.9% or in Dextrose 5%. We recommend a 1:1 dilution.

The product is a protein: HANDLE GENTLY TO AVOID FOAMING!

Avoiding foaming during product handling, preparation and administration is important, as foaming could cause the denaturation of the proteins. Once diluted, the solution for infusion is stable at 2°C to 8°C for 24 hours and at room temperature for an additional 12 hours.

Pre-medication: all patients should be well hydrated and treated with Allopurinol (300 mg per os) or a suitable alternative treatment for 12-36 hours before the first dose of therapy. One to two hours before the first administration we recommend a hydration with 500 ml of fluids.

One hour before treatment start:

- 1 g Paracetamol per os
- intravenous antihistamine (for example 1 vial = 2 mg Tavegyl).

Administration of treatment. While administering the drug for the first time, all the necessary equipment for the treatment of anaphylactic shock should be readily available.

Patients monitoring: During the first infusion the patient should be monitored. Pulse, blood pressure, temperature should be recorded every 15 minutes for the whole treatment duration and up to 2 hours thereafter.

If complications occurred during the 1st infusion, monitoring should be maintained during further infusions.

Administration of the first treatment: During the first treatment with rituximab, in case of no toxicity the infusion speed can be gradually increased every hour up to a maximum of 300 mg/h according to the following scheme. The use of an electronic infusion pump is recommended.

if WBC < 25 x 10^9/l:

0-60 minutes	50 mg/h
60-90 minutes	100 mg/h
90-120 minutes	150 mg/h
120-150 minutes	200 mg/h
150-180 minutes	250 mg/h

180 minutes - to the end	300 mg/h

if WBC ≥ 25 x 10^9/l:

0-60 minutes	25 mg/h
60-120 minutes	50 mg/h
120-180 minutes	100 mg/h
180-240 minutes	150 mg/h
240-300 minutes	200 mg/h
300 minutes - to the end	250 mg/h

In case of complications:

Stop the treatment immediately, wait until symptoms have disappeared and continue the treatment at half the previous rate.

A set of emergency medication for the treatment of an anaphylactic shock should be available.

In case patients develop infusion related symptoms it is recommended to admit them in hospital overnight for the treatment of possible late systemic side effects.

Administration of the following treatments:

For patients having experienced a life-treatening cytokine release syndrome (severe dyspnea, hypotension, confusion) the following infusion must be administered as inpatient, and only after complete resolution of all pathological signs and symptoms.

If the first treatment was well tolerated, the infusion rate of the subsequent infusions can be increased as following:

0-60 minutes	100 mg/ hour
60-90 minutes	200 mg/ hour
90-120 minutes	300 mg/hour
120 - to the end	400 mg/hour

In case of complications:

Proceed as described above.

25.13 Appendix XIII: Shipment of blood and BM samples

Two cover letters are provided at the end of the protocol for shipment of blood and bone marrow

25.14 Appendix XIV: Patient Enrollment and Identification List

This list records all patients that are registered into this trial. The list should provide patient identification at the center. This includes family name (last name), first name, initials (as used on the forms), date of birth, sex, unique patient number (UPN) in the trial, and further items, e.g. hospital record number/hospital patient chart number.

25.15 Appendix XV: Authorization List

25.16 Appendix XVI: Inventory Log (rituximab/Mabthera®)

Appendix XVII: SAKK 35/03 Patient enrollment and identification list

Protocol SAKK 35/03
Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma:
A randomized phase III trial

_____ _____

Page of

Center:

Principal investigator:

Pat No.	Initials Last / first name	Last name, first name	Address	Date of birth	Sex	Hospital chart (archive number)	UPN	Treatment Arm (A/B)	Start of treatment	Remarks (e.g. date of death)
1	☐☐☐									
2	☐☐☐									
3	☐☐☐									
4	☐☐☐									
5	☐☐☐									
6	☐☐☐									
7	☐☐☐									

Appendix XVIII: SAKK 35/03 Authorization list

Protocol SAKK 35/03 **Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial** ***This list must be kept at the center***	Principal Investigator: Center:

Name	Title	Respon-sibility*	Duties#	Signature	Initials	Start date	End date
						Day Month Year	Day Month Year
						Day Month Year	Day Month Year
						Day Month Year	Day Month Year
						Day Month Year	Day Month Year
						Day Month Year	Day Month Year
						Day Month Year	Day Month Year

***) Responsibility**

PI = Principal investigator
SI = Sub-investigator
DM= Local data manager, flying data manager
ON = Oncology nurse
OT = Other, specify:……
……..

#) Duties

1= Patient screening, selection and accrual, obtaining informed consent
2= CRF completion
3= Signing CRF
4= Reporting of Serious Adverse Events
5 = Drug accountability
6 = Other, specify: ……

Principal investigator signature:..... Date: ☐☐☐☐☐☐☐☐

SAKK 35/03 Inventory log (Mabthera®)

Protocol SAKK 35/03 **Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma:** **A randomized phase III trial** Investigator: Center:	_____ _____ Page of Person(s) dispensing drug: Initials: _____ _____ _____ _____ _____ _____

Drug name: Mabthera® Vial size: ☐ 100 mg ☐ 500 mg (For each vial size please use a separate log)

Date	Batch	Expiry date	Number of vials		UPN	Patient's initials	Balance	Initials
			Received from Roche	Dispensed for patient				

Cover letter for shipping of bone marrow and peripheral blood samples for molecular biology

2-3 ml of heparinized bone marrow

and/or

20 ml of heparinized blood

drawn at the time points stated in the Study Flow Chart / Study Assessment (see sections 17 and 25.11). The samples should be **clearly labeled and shipped EXPRESS AT ROOM TEMPERATURE**, no later than on Thursday (to avoid arrival during the weekend) to:

Francesco Bertoni, MD
Experimental Oncology,
Oncology Institute of Southern Switzerland
c/o stabile IRB, via Vincenzo Vela 6
CH-6500 Bellinzona
Email: frbertoni@mac.com / phone: +41 (0)91 8200 367 / fax: +41 (0)91 8200 397

SAKK PROTOCOL 35/03 – LABORATORY FORM

Patient's initials: Last Name ☐☐ First Name ☐ UPN: ☐☐☐

Date of Birth Day ☐☐ Month ☐☐ Year ☐☐☐☐ Date sample taken Day ☐☐ Month ☐☐ Year ☐☐☐☐

Shipped Sample type: ☐ Blood ☐ Bone Marrow

White blood cells ☐☐☐.☐ 10^9/l Lymphocytes percentage ☐☐%

Time point Baseline ☐ After induction ☐ at month 6 ☐ at month 12 ☐

Every 12 months during maintenance or in follow-up ☐ at progression/relapse ☐

Responsible physician: _____ Center: _____ Phone Number: ☐☐☐☐☐☐☐☐☐☐☐

Date Day ☐☐ Month ☐☐ Year ☐☐☐☐ **Signature:** _____

Cover letter for shipping of peripheral blood samples for immunophenotyping

3-4 ml of peripheral blood in EDTA tubes

drawn at the time points stated in the Study Flow Chart / Study Assessment (see sections 18 and 25.11). The samples should be **clearly labeled and shipped EXPRESS AT ROOM TEMPERATURE immediately after sample collection. Do not collect and send samples on Friday, Saturday, and the day before national holidays. Send sample including this letter, appropriately covered, to:**

FACS-Labor
Zentrum für Labormedizin
Kantonsspital Aarau
CH-5001 Aarau
Switzerland

Tel: +41 (0)62 838 5320 or +41 (0)62 838 5310 / E-mail: ingmar.heijnen@ksa.ch

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SAKK PROTOCOL 35/03 – LABORATORY FORM

Patient's initials: Last Name First Name ☐☐ ☐ UPN: ☐☐☐

Date of Birth Day Month Year ☐☐ ☐☐ ☐☐☐☐ Sex f/m ☐ Date sample taken Day Month Year ☐☐ ☐☐ ☐☐☐☐

Time point Baseline ☐ After induction ☐ at month 6 ☐ at month 12 ☐

Every 12 months during maintenance or in follow-up ☐ at progression/relapse ☐

Responsible physician: _____ Center: _____

Phone number: ☐☐☐☐☐☐☐☐☐☐☐

Date Day Month Year ☐☐ ☐☐ ☐☐☐☐ **Signature: _____**