Efficacy of maintenance therapy with rituximab after induction chemotherapy (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for autologous stem cell transplantation

A RANDOMIZED PHASE III STUDY OF THE *EUROPEAN MCL NETWORK*

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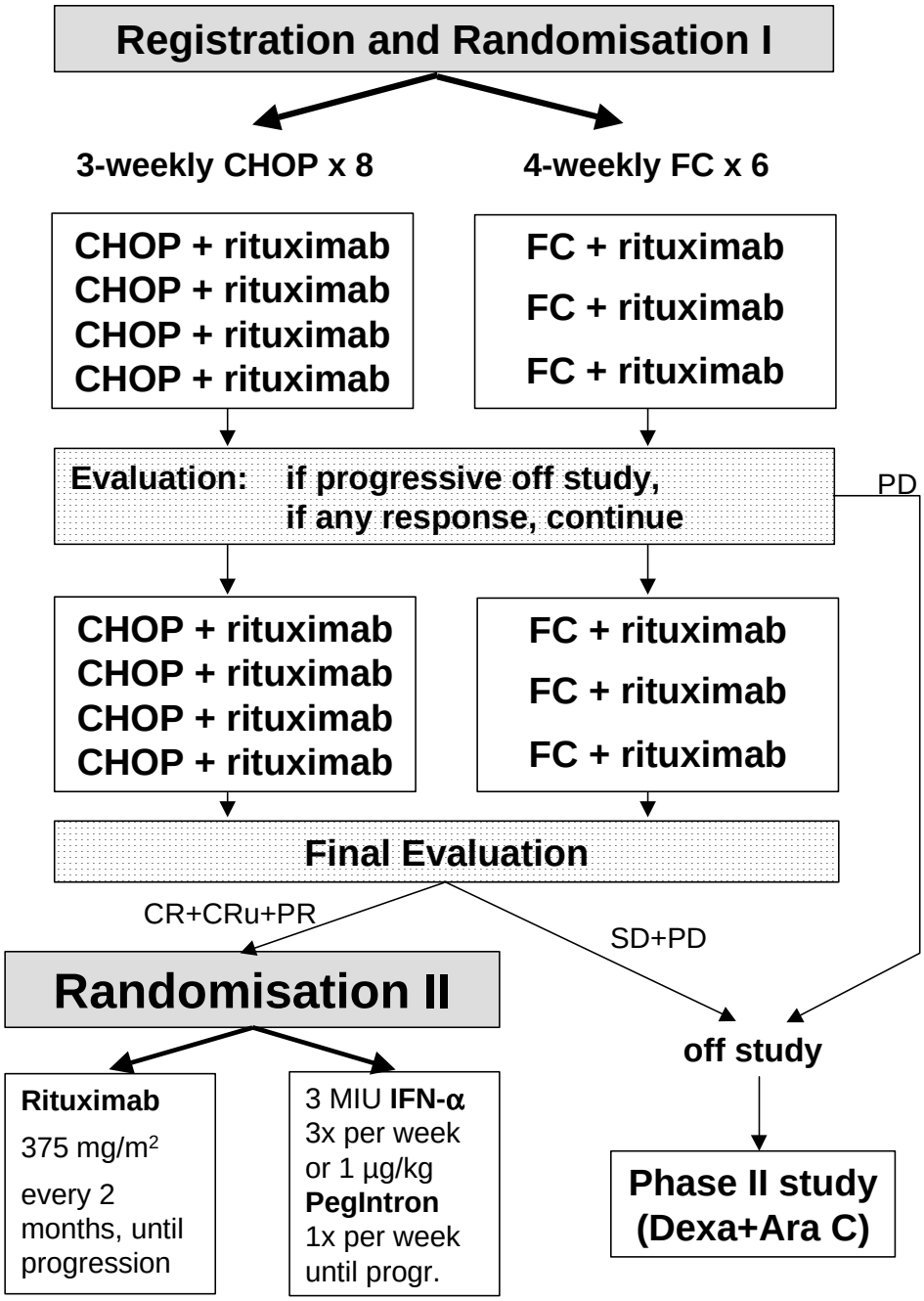
1. Trial design



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3. Synopsis

Title	Efficacy of maintenance therapy with rituximab after induction chemotherapy (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for stem cell transplantation
Study design	Prospective, multicenter, randomised phase III trial of the *European MCL Network*
Primary study objectives: - first randomisation - second randomisation:	 Reduction of lymphoma mass measured by the CR rate progression-free survival after end of initial chemotherapy
Secondary study objectives	Overall survival after start/end of initial therapy
Inclusion criteria	- Patients with histologically confirmed mantle cell lymphoma - advanced stages II-IV - previously untreated - 65 years and older or 60-65 if not eligible for high dose chemotherapy
Treatment	Initial cytoreductive therapy: randomisation between 8 x CHOP-21 + rituximab versus 6 x FC-28 + rituximab For CR/PR patients second randomisation between 2-monthly rituximab 375 mg/m^2 versus Interferon-α 3x 3M IU or Peg-Intron 1 μg/kg weekly until progression
Number of study centres	unlimited; centres can join the ongoing study after authorisation
Number of patients	Max. 570 patients
Duration of recruitment	4-6 years
Planned start	01-1-2004

4. List of coordinators and study administrative structure

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4.1 Pathology review

One stained (hematoxylin and eosin) slide of a representative lymph node biopsy or extranodal site together with the paraffin embedded block and/or 10 unstained sections on APES-coated slides should be sent to the annotated pathologists below (participants of the European MCL Network Pathology Group). The diagnosis of the local pathologist will be used for registration and start of treatment. However, it is strongly advised – given the high percentage of discordances – to have the material reviewed before entry in the study.

A central pathology review will be performed by the European MCL Network Pathology Panel. The review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of mantle cell lymphoma (both by morphology and immunophenotyping including CD5, CD10, CD20, CD23, BCL2 and Cyclin D1), and recording of the morphological variants including prognostic factors such as Ki67 expression. Finally, it is recommended to have for each case freshly frozen material available for the design of clone-specific immunoglobulin primers to be used for minimal residual disease (MRD) analysis (chapter 9.2.2). If the laboratory has no facility to store these materials, these should be sent to the laboratory of one of the annotated pathologists.

4.2 Overview of reference pathologists

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Sweden	Refer to E. Rafkier (Denmark)
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Other centers may refer to the reference pathologist of their choice.

5. Background

Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma (MCL) represents a B cell non-Hodgkin's lymphoma with – in addition to histomorphology - well-defined phenotypic and genotypic characteristics[1; 2]. Amongst these, the cells carry the immunophenotype of normal mantle cells (pan B markers, strong Ig expression of IgM/IgD, co-expression of CD5 in the absence of CD23). All MCL cases harbour a t(11;14) translocation, caused by rearrangement of bcl-1 and overexpression of cyclin D1[3]. The outlook for patients with MCL is dismal. Prognostic factor analyses showed that also for patients with MCL, the IPI risk profile (in which age is an important factor) is predictive, which clarifies why elderly patients with MCL especially have a very poor prognosis[4; 5].

The first randomised study on MCL was initiated by the European MCL Intergroup Working Party, now renamed as European MCL Network[6]. In this study, patients below the age of 65 were randomised upfront between CHOP-like induction courses followed by IFN-alpha maintenance (arm 1) versus CHOP-like induction courses followed by DexaBEAM, stem cell harvest and autologous stem cell transplantation (arm 2). The trial was monitored by a one-sided sequential test. Data were disclosed to the participants after this procedure had decided in favour of PBSCT. At the statistical evaluation in June 2001 (based upon 130 out of the 180 randomised patients), it appeared firstly that the percentage of patients obtaining a complete or partial remission (CR/PR) after the induction with 6 CHOP courses was low, namely 24% and 52% respectively. Secondly, it was shown that the more intensive arm 2 (including autologous stem cell transplantation) showed a significantly better Progression Free Survival (PFS at 2 years arm 1: 48% versus arm 2: 75%), although the Overall Survival curves for the patients who obtained a complete or partial remission (CR/PR) after the CHOP induction were not (yet) significantly different. Importantly, the PFS curves did not show a plateau thus far. Thirdly, the control arm using IFN maintenance showed that only 25% of the patients were without progression at 3 years.

Elderly patients

For elderly patients, autologous stem cell transplantation is considered too toxic. This means that the chance to improve upon the disease-free survival (and preferably overall survival) will be very much reduced compared to younger patients. In addition, the impact on the quality of life might be more important for these elderly patients with a presumably worse outcome than for a younger cohort.

Rituximab, anti-CD20 therapy

Presently, several other studies are ongoing incorporating new drugs and treatment policies to improve upon the results for MCL. One of the potentially important drugs is the chimeric monoclonal antibody anti-CD20 rituximab. Administration of a single infusion results in the depletion of over 90% of the circulating normal and malignant B cells from the peripheral blood from 24 hours after the infusion for as long as 8 days. Blood stem cells are not affected by anti-CD20 and the agent is not myelosuppressive. As a single agent the toxicity of rituximab is moderate and transient[(7)]. In elderly patients with aggressive B cell NHL, the addition of rituximab to CHOP resulted in a 10-15% improvement of PFS[(8)].

In nearly all mantle cell lymphomas there is a high expression of CD20. Rituximab has documented activity in MCL given both as single drug as well as in combination with conventional chemotherapy, in both untreated as previously treated patients with MCL[(9; 10)]. Moreover, the GLSG group has run a trial (CHOP with or without rituximab) for so-called „low grade“ malignant NHL patients in which 82 patients with MCL have been included. The results from this trial for the MCL patients show that the percentages CR/OR after CHOP were 10% / 71% versus the significantly higher 45% / 90% after CHOP + rituximab ($p < 0.001$ / $p=0.031$) [(11)]. Similarly, in relapsed MCL, the addition of Rituximab resulted in a 30% increase of the CR rate and a 20% improve of overall response; interestingly, these differences resulted in a significantly improved overall survival in patients with relapsed MCL [(12,13)].

FC chemotherapy scheme

Other chemotherapy combinations, attractive for elderly patients with MCL, which have been studied in the GLSG group are drugs like fludarabine in a combination with

cyclophosphamide and/or mitoxantrone (FC or FCM) [12]. Fludarabine on its own is able to down-regulate bcl-2 production in a minority of $CD5^+$ B cell malignancies, which seems to be related to clinical response[14]. The drug showed activity in several phase II studies[15-17] with a complete response rate of 28% in untreated MCL[17]. Fludarabine-containing combinations achieved superior overall response rates around 60% in relapsed MCL [18,19]. The GLSG performed a study with additional rituximab and FCM on patients with *relapsed* follicular lymphoma or MCL, comparing FCM with rituximab-FCM[12]. Although the numbers of MCL patients treated with the FCM combination was rather low, the efficacy is promising: 33% of these relapsed patients obtained a CR versus 0%) when R-FCM was compared with FCM alone (p=0.003). Accordingly, there was a 20% increase of overall response (62% vs. 43%; p=0,179). After a combined immuno-chemotherapy. Most importantly, a significantly improved overall survival was observed in the R-FCM arm (p=0,005). Therefore, there are many arguments to assume that FC with rituximab will be more effective than FC alone without any increase in major adverse effects. Several publications have shown promising data with the combination of fludarabine and cyclophosphamide only (FC), thus omitting the risk of cardiotoxicity in elderly patients. Moreover, Zucca *et al*[20] and Meuser *et al*[21] could not demonstratethat addition of anthracyclins did improve the survival in MCL patients with poor prognostic factors (such as age above 60 years). The German CLL group used for an age group of median 59 years, a 3 day scheme of fludarabine 30 mg/m^2 and decreased the cyclophosphamide dose of 3 x 300 mg/m^2 to 3 x 250 mg/m^2 thus avoiding grade 3 and 4 infections, although myelotoxicity remained severe[22].

Maintenance therapy

In the past, several studies[23] suggested in a retrospective analysis that IFN-alpha maintenance at a dose of 3 x 3 MIU/week for 2 years improved the PFS and OS for patients with MCL. Similar results have been obtained by the GLSG using a similar dose IFN schedule. This has been the reason that in the European MCL phase III Study this maintenance scheme was added to the control CHOP arm as a kind of „gold standard“ to which the PBSCT was compared. On the other hand, especially in elderly patients, the toxic side effects of IFN (flu-like syndrome, depression, and wasting syndrome) may result in a significant dose reduction. Recently, a pegylated form has been applied in malignant lymphoma which has a more favourable duration of side

effects due to a once weekly injection only [24]. Therefore, instead of conventional interferon, this pegylated form may be applied at an estimated equivalent dose of 1µg/kg weekly[25]. It is important to realise, however, that the first Progression free survival curves of this control arm showed that at 3 years only 25% of the patients are free of progression, and that all patients have relapsed after 3,5 years. With the new compound rituximab, it is attractive to study whether addition of rituximab as maintenance after induction therapy can improve upon this.

6. Study objectives

6.1 Objectives of the trial

1. To test in elderly patients with advanced mantle cell lymphoma, whether rituximab plus a combination of fludarabine with cyclophosphamide (6 FC cycles) results in a higher reduction of lymphoma mass measured by the percentage of CR than rituximab combined with the standard chemotherapy scheme (8 CHOP cycles).

2. To compare maintenance therapy with rituximab with maintenance with interferon-alpha or pegylated interferon for progression free survival, after 2 different regimens of induction chemo-immunotherapy in elderly patients with mantle cell lymphoma.

6.2 End points

First randomisation:	percentages of complete responses after initial cytoreductive chemotherapy.
Second randomisation:	progression free survival in CR or PR after initial cytoreductive chemotherapy.
For the end of observation:	Overall survival after start/end of initial cytoreductive chemotherapy.

6.3 Stratification factors

Randomisation will be stratified for the following factors:

Study group/association of centre:

- GELA
- GLSG
- HOVON
- Nordic Lymphoma Group
- Centres not associated to one of these study groups

Age 60-65 versus >65 year and older

International Prognostic Index (IPI) with following risk factors:

- age above 60 years
- stage III and IV
- LDH serum level over normal range of the respective laboratory
- performance-status (ECOG-status) >1
- more than 1 extra nodal involvement

Stratification-groups: 1 or 2 risk factors (low and low intermediate risk) vs.
3 to 5 risk factors (high or high intermediate risk)

Induction scheme (for second randomisation only):
stratification-groups: R-FC vs. R-CHOP

Result of initial cytoreductive therapy (for second randomisation only):
stratification-groups: CR/CRu vs. PR

7. Treatment schedule

7.1 Rituximab administration

Rituximab will be added to the chemotherapy course *as soon as the number of circulating lymphoma cells is <10x 10 ^{9}/l***,** to circumvent direct toxicity of this drug which is more frequent in leucemic lymphoma. Before each consecutive course it will be reconsidered if this criterion is fulfilled and Rituximab can be added. It is allowed to

postpone rituximab for 1-2 weeks, if it is not possible to administer the drug at day 1. However, not administered Rituximab treatments will not be reconstituted.

For elderly patients, it is strongly advised to give the rituximab infusions in an inpatient setting for the first time. If no adverse events have occurred the following transfusions can be given in an outpatient ward. A peripheral (IV) line will be established. Vital signs (blood pressure, pulse, respiration, and temperature) should be monitored every 15 minutes during the first hour or until stable and then hourly until the infusion is discontinued and vital signs are stable. Premedication with paracetamol and/or antihistaminics (e.g. Tavegil or diphenhydramine) is strongly advised. For patients receiving CHOP, the oral prednisone dose should be taken at least one hour before the rituximab infusion, or given intravenously. Corticosteroids are strongly advised (25 – 50 mg hydrocortisone intravenously, or 5 mg dexamethasone intravenously) for patients receiving the FC combination, which lacks the 5 day prednisone gifts from the CHOP course. The initial dose of rituximab should be 50 mg/hr for the first hour. If no adverse event is seen, the dose may be escalated in 30 minutes intervals with increment steps of 50 mg/hr, to a maximum of 400 mg/hr. Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. When any of the following events is noted, antibody infusion should be temporarily discontinued, the patient should be observed and the severity of the adverse events should be evaluated:

- Fever > 38.5° C
- Mild/moderate rigors
- Mild/moderate mucosal congestion or edema
- Drop in systolic blood pressure > 30 mm Hg
- dyspnoe and bronchospasm

The patient should be treated according to the best available local practices and procedures. Following observation, if the patients systems improve, the infusion should be continued at 1/2 the previous rate. Following the antibody infusion, the IV line should be kept open for medications. If there are no complications, observation may be discontinued after one hour . If complications occur during infusion, the patient should be observed for two hours after the completion of the infusion. If no adverse event is seen with the previous infusion, the infusion rate at the start of following infusions can be increased to 100 mg/hr and if no further adverse event is observed the infusion rate

can be increased with 30 minutes intervals with increment steps of 50 mg/hr to a maximum of 400 mg/hr.

7.2 CHOP chemotherapy

CHOP + Rituximab

Agent	Dose/day	Route	Days
Rituximab	375 mg/m^2, max. 750 mg	IV	1 (eventually day 0)
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin	50 mg/m^2	IV	1
Vincristine	1.4 mg/m^2, max. 2 mg	IV	1
Prednisone	100 mg total	orally	1, 2, 3, 4, 5

Rituximab will be given IV at a dose of 375 mg/m^2 (max. 750 mg) at the first day of CHOP, if the circulating number of lymphoma cells is <10x 10^9/l (see 7.1). Prednisone, according to CHOP dose, will be given 1 hour prior to rituximab; after rituximab infusion cyclophosphamide, doxorubicin and vincristine are given. It is allowed to give rituximab one day before the CHOP chemotherapy, but prednisone should always be given before the rituximab.

7.3 Dose modifications of CHOP

No dose modification will be made in the first course. During the next courses, modifications of the treatment schedule will only be made if:

- *Neurotoxicity* (peripheral neuropathy, severe obstipation/paralytic ileus): adapt vincristine according to the discretion of the treating physician.
- *Myelosuppression*: if WBC <4x 10^9/l or thrombocytes <100x 10^9/l at the day of the next course, postpone 1 week; if after 1 week insufficient recovery, adapt according to scheme below.

WBC x 10^9/l	thrombocytes x 10^9/l	Cyclophos-phamide	Doxorubicin	Vincristine	Prednisone	Rituximab
>3	>100	100%	100%	100%	100%	100%
2 – 3	>100	75%	75%	100%	100%	100%
1 – 2	50-100	50%	50%	100%	100%	100%
<1	<50	0%	0%	100%	100%	100%

Dose reduction will be calculated according to the doses given in the previous cycle. In case of severe myelosuppression with granulocyte counts < 1.0x 10^9/l and/or thrombocyte counts <50x 10^9/l as assessed on two consecutive days but recovery to WBC >3.0x 10^9/l after 3 weeks, it is strongly advised to reduce the dose of R-CHOP to 75% in cyclophosphamide and 75% in doxorubicin in subsequent cycles. This reduction of dose can be omitted if the severe myelosuppression can be assumed to be the result of an initial significant bone marrow involvement.

7.4 Fludarabin/cyclophosphamide chemotherapy

FC + Rituximab

Agent	Dose/day	Route	Days
Rituximab	375 mg/m^2, max. 750 mg	IV	1 or at day 0, before FC
Fludarabin	30 mg/m^2	IV	1, 2, 3
Cyclophosphamide	250 mg/m^2	IV	1, 2, 3

Rituximab will be given IV at a dose of 375 mg/m^2 (max. 750 mg) at the first day of FC, if the circulating number of lymphoma cells is <10x 10^9/l (see Chapter 7.1). After rituximab infusion cyclophosphamide and fludarabin are given. It is allowed to give rituximab one day before the chemotherapy, preferably preceded by a gift of 100 mg predniso(lo)n. Based upon pharmacokinetic datacyclophosphamide should be given at least *one hour after* fludarabin.

7.5 Dose modifications of FC

No dose modification will be made in the first course. During the next courses, modifications of the treatment schedule will only be made if myelosuppression occurs: if WBC <4x 10^9/l or thrombocytes <100x 10^9/l after 4 weeks, postpone 1 week; if after 1 week insufficient recovery, adapt according to scheme below.

WBC x 10^9/l	thrombocytes x 10^9/l	Fludarabine	Cyclophos-phamide	Rituximab
>3	>100	100%	100%	100%
2-3	>100	75%	75%	100%
1-2	50-100	50%	50%	100%
<1	<50	0%	0%	100%

Dose reduction will be calculated according to the doses given in the previous cycle. In case of severe myelosuppression with granulocyte counts <1.0x 10^9/l and/or thrombocyte counts <50x 10^9/l as assessed on two consecutive days but recovery to WBC >3.0x 10^9/l after 4 weeks, it is strongly advised to reduce the dose of R-FC to 75% in cyclophosphamide and 75% in fludarabin in subsequent cycles. This reduction of dose can be omitted if the severe myelosuppression can be assumed to be the result of an initial significant bone marrow involvement.

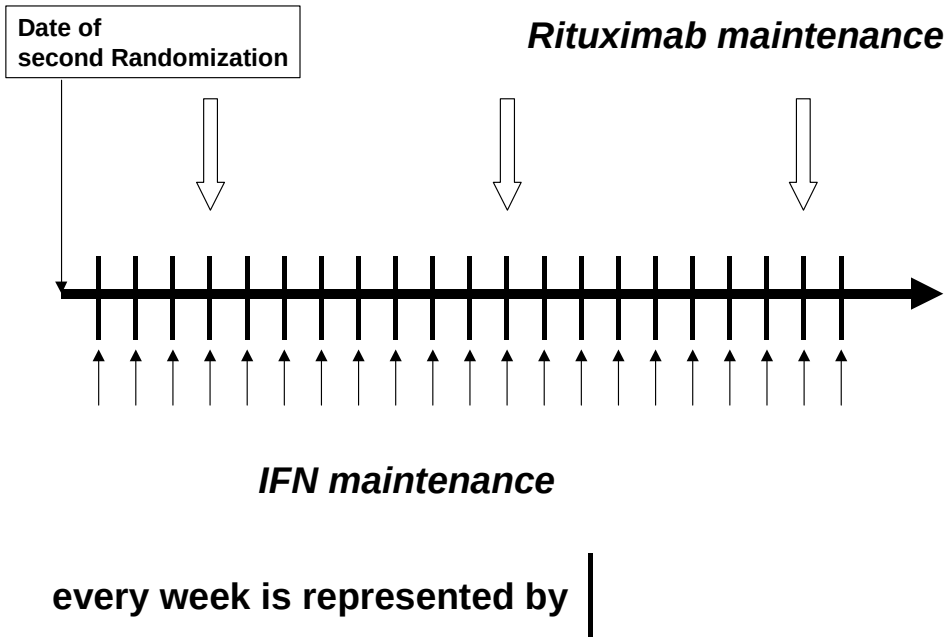
7.6 Use of G-CSF

Use of hematopoietic growth factors is at the choice of each individual investigator. The use of G-CSF might be considered if grade 4 (severe neutropenia) or febrile neutropenia after any cycle of chemotherapy has occurred. G-CSF should be started at day +2 after CHOP, or at day +4 after FC and continued for 7-10 days, or until the granulocytes have risen to >3x 10^9/l. G-CSF should never be given simultaneously with the chemotherapy.

7.7 Maintenance therapy

Maintenance therapy should start directly after the date of randomisation according to

the following scheme:



Interferon maintenance (thin closed arrow) starts within the first month after randomization either IFN-α 3x 3 M IU or PegIntron 1 μg/kg per week. Rituximab maintenance (big open arrow) is given every 2 months starting at month +1 after randomization.

7.7.1 IFN-alpha

Interferon-alpha will be given at a dose of 3 million units, 3 times a week. Interferon-alpha causes toxicity which can be in part be reduced by given it once a week in the pegylated form. For this study, the pegylated formula Interferon-alpha 2b (PEG-Intron) can be used. One microgram/kg once a week is equivalent to the classical 3x 3 MIU/week[25]. PegIntron is available as dry powder or as pre-filled injection files at doses of 50, 80, 100, 120 or 150 microgram. The nearest dose should be used when 1 microgram/kg is calculated. Given the large differences, it is not allowed to use the pegylated formula Pegasus, because equivalence doses have not yet been established. If the classical administration (3x 3 MIU per week) is preferred, either interferon alpha 2b or alpha 2a may be given. Both drugs, however, will not be reimbursed by the

industry. The most frequent adverse effects with PEG Intron are flu-like symptoms, redness at the injection site, headache, and fatigue/malaise. All these adverse events were mild in severity. PEG Intron is available as powder with dissolving fluid, or as ready-to-use injection pen. In both cases, it is advised to take 500–1000 mg paracetamol before the s.c. injection.

Dose of interferon-alpha:	3x 3 MIU per week classical type IFN-alpha, or once a week 1 microgram/kg PegIntron s.c. rounded up at 50, 80, 100, 120 or 150 microgram.

Dose adaptations:

in case of any CTC grade 2 - 3 toxicity:	reduce by 30-50 percent
in case of any CTC grade 4 toxicity:	interrupt until restoration, resume at about 50%, and increase gradually if tolerated

For classical interferon-alpha the number of applications per week can also be altered in case of dose reduction.

7.7.2 Rituximab

One month after the second randomisation, the gift of rituximab should be given at a dose of 375 mg/m^2, intravenously, following the guidelines given in 7.1. The next dose will be repeated at a 2 months interval. For toxicities, see 7.1.

7.8 Supportive care

Patients should receive full supportive care according to the local guidelines, including allopurinol and sodium bicarbonate (only if heavy tumour loads are present) at start of the induction chemotherapy, transfusions of blood and blood products, antibiotics, anti-emetics, etc. where applicable to the discretion of the physician. The use of prophylactic antibiotics is recommended, but not mandatory. Dose adaptions or postponements of the therapy, dosage, and dates of treatment should be recorded on the CRF. Patients who are receiving or have received the FC scheme should be supported by irradiated blood products to avoid transfusion-related graft versus host disease up to 6 months

after the last gift of fludarabine. Moreover, given the fact that both T cell function as well as B cell function are temporarily disrupted when FC and rituximab are combined, it is important to be aware of the potentially immuno compromised status of the patients.

7.9 Cytoreductive Pre-Phase

Patients with relevant B-symptoms or raising peripheral lymphocyte counts but incomplete diagnostic reports may receive a pre-phase therapy of one single dose of vincristin (1.4 mg/m^2, max. 2 mg) and 100 mg prednisone per day for 1 to 5 days before registration in the study. The pre-phase therapy should not be started before all necessary biopsies were taken. In patients who will receive CHOP in further treatment, the vincristin dose in the first cycle should be omitted.

8. Study population

8.1 Eligibility for registration

All eligible patients have to be registered before start of treatment.

8.1.1 Inclusion criteria

- Histologically proven mantle cell lymphoma according to the WHO classification, preferably confirmed by central pathology review beforehand
- Clinical stage II, III or IV
- Previously untreated patients
- Above the age of 65 years and older
  or patients at the age between 60 and 65, if not eligible for high dose chemotherapy
- WHO performance ≤ 2
- Informed consent according to ICH/EU GCP and national/local regulations
- Measurable disease. If e.g. only BM infiltration, patients can only undergo a second randomization if a CR is obtained

8.1.2 Exclusion criteria

- WHO performance of 3 or more
- Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies
- Leukocytes <2.0x 10^9/l or thrombocytes <100x 10^9/l, unless clearly related to MCL bone marrow infiltration
- Patients previously treated for lymphoma
- Patients without measurable lesions; if e.g. only bone marrow infiltration, patients may be included, but can only undergo a second randomization in case of CR
- Patients with stage I disease
- Patients with central nervous system involvement
- Patients with a history of autoimmune hemolytic anaemia or autoimmune trombocytopenia
- Patients with serious cardiac disease (uncontrolled arrhythmias, unstable angina, severe congestive heart failure)
- Patients with serious pulmonary, neurological, endocrinological or other disorder interfering with full dosing of CHOP or FC chemotherapy
- Liver enzymes >3x normal or bilirubin >2.5x normal (not due to lymphoma)
- Creatinine >2x normal value, corrected for age and weight (not due to lymphoma)
- Patients with unresolved hepatitis B or C infection or HIV positive infection
- Uncontrolled infection
- Patients with a serious depression that needed therapy within the last 5 years
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Concomitant or previous malignancies other than basal cell or squamous cell skin cancer, in situ cervical cancer and other cancer for which the patient has been disease-free for at least 5 years

9. Diagnostic procedures

9.1 Evaluation of treatment response

Halfway the chemotherapy period (after the 4th CHOP cycle or 3rd FC cycle), patients should be evaluated to decide whether the initiated chemotherapy results in any response. If the lymphoma is progressive, the patient goes off protocol. The final clinical response rate will be determined at 4 weeks after the last cycle of CHOP or FC, directly before the second randomisation, and is defined as the percentage of patients achieving a partial response (PR) or complete response (CR) (response criteria according to the „International workshop to standardise response criteria for Non-Hodgkin's lymphomas" [see 13.2]. CR-unconfirmed (CRu) will be categorised as PR. During the maintenance therapy an evaluation should take place twice a year during the first 2 years, and at the time of progression.

9.2 Baseline evaluations

9.2.1 Clinical Investigations

The histological examination of representative diagnostic material (lymph node, other involved soft tissue or bone marrow only if lymph node material is not available) must be performed within 3 months prior to therapy onset. The diagnosis will be reviewed by one of the panel pathologists (see 4.1). It is strongly advised to have the material reviewed before registration of the patient. The following baseline evaluations must be performed within 6 weeks prior to the first administration of therapy (physical examination and basic laboratory examination within 2 weeks):

- Medical history and demographic data (including height and body weight)
- Physical examination (including general physical examination, consultation ENT-specialist, temperature, blood pressure, heart rate, WHO performance status [see Appendix A]
- ECG, optional: echocardiography
- Chest X-ray
- CT of the cervical region (neck), chest, abdomen and pelvis for staging
- Optional abdominal ultrasound.

- Endoscopy or other investigations for extranodal localisations, if clinically indicated
- Bone marrow biopsy for cytology, histology and optional immunophenotyping (CD20/CD5 staining)
- Clinical laboratory examination (within 2 weeks):
  - CBC with differential and platelet count
  - Immunophenotyping (double staining CD19/CD20/CD5)
  - Glucose, sodium, potassium, creatinine, BUN, uric acid, ASAT (SGOT), ALAT (SGPT), alkaline phosphatase, γ-GT, bilirubin, LDH, total protein, albumin, IgG, IgM and IgA
  - Direct Coombs test
  - Urine analysis: pH-value, erythrocytes, total protein, glucose (dipstick)
  - Antibody status: HIV, HBV, HCV
- 20 ml EDTA blood / 5 ml EDTA bone marrow and 20 ml heparin blood/ 5 ml heparin bone marrow for MRD/biological studies, see 9.2.2
- Check of inclusion/exclusion criteria
- Obtain patient's written informed consent

9.2.2 European MCL Research Network/Minimal Residual Disease (MRD)

Based on this previously established European MCL Intergroup Working Party and the European MCL Pathology Panel, in 2001 a European MCL research network has been established with meanwhile 18 participants from 8 different countries who focus especially on the characterisation of molecular and biological risk factors in MCL. This scientific network brings together experts of cytogenetics, molecular and cell biology and is structured into 4 differentially focussed work packages, each of them representing an international collaboration of various study groups:

I. Primary genetic alterations and markers of maturation

This project further characterises the initial genomic rearrangements of MCL, the t(11;14)(q13;q32), and the immunoglobulin gene rearrangements, to define the biological and prognostic relevance of these primary events.

II. Cell cycle dysregulation in MCL

As the proliferation activity has been identified as the most important prognostic factor in

MCL, various regulators of the cell cycle machinery will be analysed to define the interactions and the functional hierarchy of various genetic alterations in MCL including the $p16^{INK4A}$-cyclin D1/cdk4-pRb pathway as well as the $p14^{ARF}$-MDM2-p53-$p21^{WAF1}$ pathway.

III. Secondary alterations in MCL

As overexpression of cyclin D1 alone is not sufficient for the development of clinical disease, this project will screen for alterations on the DNA, RNA and protein level applying well established as well as innovative techniques like RNA array and proteome analysis. In addition, distinct genetic alterations will be further characterised.

IV. Functional studies of MCL

The well-known chemotherapy resistance of MCL will be elucidated with special emphasis on the deregulation of apoptosis and proliferation using different cell culture and transfection techniques. Within this research network, biological parameters like proliferation indices and associated molecular alterations have been identified as the most important prognostic factors superior to morphological criteria.

V. Minimal residual disease

There are strong hints from recently published data that minimal residual disease (MRD) detection may play a role as a prognostic factor in patients with MCL. Aim of MRD analysis within this study protocol is the monitoring of MRD by quantitative TaqMan PCR (RQ-PCR) targeting clonal immune gene rearrangements or t(11;14) translocation to evaluate the prognostic impact of MRD on disease free survival and long-term remission of patients with mantle cell lymphoma. This real time PCR method is sensitive enough to detect 1 lymphoma cell in the background of 10^4-10^5 normal cells. PCR-analysis will be performed from peripheral blood (10 ml EDTA blood) and bone marrow (3-5 ml EDTA bone marrow aspirate). As a prerequisite for molecular assessment of MRD using RQ-PCR in usual diagnostic material, lymph node, peripheral blood and bone marrow has to be sent <u>before</u> start of any treatment to determine the individual patient-specific DNA - sequence of the malignant clone.

Additional FACS analysis will be performed at every time point of MRD detection to evaluate the B-cell background during treatment with Rituximab. Therefore it is essential to send Heparin blood or bone marrow for FACS analysis together with EDTA blood and bone marrow for FACS analysis at every time point of MRD investigation.

*The results of MRD will **not** be incorporated into the response evaluation nor influence the management of the patient.*

Sample collection

Time points for sample collection for the European MCL Research Network/Biomed II MRD project are:

Prior induction: for all patients before treatment:
20 ml EDTA blood / 5 ml EDTA bone marrow
20 ml heparin blood / 5 ml heparin bone marrow

optional: after 4x R-CHOP/3x R-FC

Post induction: after induction with R-CHOP or R-FC
20 ml EDTA blood / 5 ml EDTA bone marrow
20 ml heparin blood / 5 ml heparin bone marrow

Follow-up: 2, 4, 6, 8 … months during Rituximab or IFN maintenance:
at 2-months intervals: 10 ml EDTA blood / 10 ml heparin blood

at 6-months intervals: 20 ml EDTA blood / 5 ml EDTA bone marrow
20 ml heparin blood/ 5 ml heparin bone marrow

Samples with the completed molecular form (Monday to Thursday by express mail) should be sent to the respective national reference labs where quantitative PCR-analysis will be centrally performed:

9.2.3 Overview of addresses of a selected list of national reference laboratories:

Country	Name and address
Denmark **Finland** **Norwegian** **Sweden**	Dr. N. Andersen Dept. of Hematology Lab. 4041 Rigshospitalet Blegdamsvej 9 DK 2100 Copenhagen OE Denmark. Phone: +45-35-451146 Fax: +45-35-454841

Country	Name and address
France	Prof. Dr. Elizabeth Macintyre, M.D. Laboratoire d'Hematologie Tour Pasteur, 2ème étage, Porte 14 Hôpital Necker-Enfants Malades 149, rue de Sevres 75743 PARIS CEDEX 15 - France Phone. +33-1-44494947 Fax. +33-1-44381745
Germany	Dr. C. Pott University Hospital Kiel Dept. of Medicine II Chemnitzstrasse 33 24116 Kiel Phone +49-431-1697-1268 Fax. +49-431-1697-1264
Netherlands	Dr. J.J.M. van Dongen Erasmus University Medical Center Rotterdam Immunology/Molecular Unit Dr. Molewaterplein 50 Rotterdam 3015 GE The Netherlands Phone: +31-10-4088094
Spain	Dr. E. Campo Unitat d'Hematopatologia Hospital Clinic Villarpel 170 E-09036 Barcelona Phone: +349-322-7-5450/5572 Fax: +349-322-7-5454

9.3 Observations during induction chemotherapy

Directly before each new chemotherapy course the following items need to be checked:

- Physical examination, including disease related symptoms, vital signs and WHO performance status [see Appendix A]
- Documentation of adverse events
- Clinical laboratory examination:
  - CBC with differential and platelet count
  - Sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH

Any patient who is progressive during initial chemotherapy therapy should go off study

9.4 Midterm evaluation during chemotherapy

To avoid unnecessary continuation of therapy, after 4 R-CHOP cycles or 3 R-FC cycles the response of the patient should be evaluated by the following examinations:

- Physical examination, including disease related symptoms, vital signs and performance status
- Documentation of adverse events
- Chest X-ray
- CT of involved nodal areas, especially assessment of measurable lesions
- Endoscopy or other investigations for extranodal localisations, if indicated
- Bone marrow histology, cytology and (optional) immunophenotyping if initial BM involvement
- Clinical laboratory examination:
  - CBC with differential and platelet count
  - Sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH
- Optional: 20 ml EDTA blood / 5 ml EDTA bone marrow and 20 ml heparin blood/ 5 ml heparin bone marrow for MRD/biological studies, see 9.2.2

9.5 Evaluation at the end of induction chemotherapy

- Before the second randomisation, the patient need to be evaluation to assess the response:
- Physical examination, including disease related symptoms, vital signs and performance status
- Documentation of adverse events
- Optional: ECG, echocardiography if clinically indicated
- Chest X-ray
- CT of involved nodal areas, especially assessment of measurable lesions
- Abdominal ultrasound (optional)
- Endoscopy or other investigations for extranodal localisations, if indicated
- Bone marrow histology, cytology and (optional) immunophenotyping if initial BM

involvement

- Clinical laboratory examination:
  - CBC with differential and platelet count
  - Immunophenotyping (double staining CD19/CD20/CD5)
  - Sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH
- 20 ml EDTA blood / 5 ml EDTA bone marrow and 20 ml heparin blood/ 5 ml heparin bone marrow for MRD/biological studies, see 9.2.2

9.6 Eligibility criteria for second randomisation

- Complete or partial remission after chemotherapy induction. Patients without measurable lesion e.g. only bone marrow involvement have to be in complete remission
- WHO performance ≤ 2
- No serious pulmonary, neurological, endocrinological or other disorder interfering with maintenance therapy
- No serious depression that needed therapy within the last 5 years
- White blood cell count >3.0x 10^9/l
- Platelet count >100x 10^9/l
- Creatinine <2x normal value
- Bilirubin <2.5x normal value
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

9.7 Investigations during maintenance therapy

During maintenance therapy with IFN or rituximab, it is important to evaluate whether the patient is still responsive, has not developed toxicity, and has not relapsed. Therefore, the following control scheme has to be followed:

9.7.1 Routine controls

Outpatient visit at month 1, 2 and 3, followed by a visit at least every 2 months. At every visit, the following should be monitored:

- Physical examination, including disease related symptoms, vital signs and performance status
- Documentation of adverse events
- Clinical laboratory examination:
  - CBC with differential and platelet count
  - Sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH
- Every 2 months: 10 ml EDTA blood / 10 ml heparin blood for MRD/biological studies, see 9.2.2

9.7.2 Response evaluation every 6 months

- Physical examination, including disease related symptoms, vital signs and performance status
- Documentation of adverse events
- Chest X-ray.
- CT of involved nodal areas, especially assessment of measurable lesions.
- bone marrow biopsy If clinically indicated to confirm the continuation of a CR/PR
- Clinical laboratory examination:
  - CBC with differential and platelet count
  - Immunophenotyping (double staining CD19/CD20/CD5)
  - sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH
- 20 ml EDTA blood / 5 ml EDTA bone marrow and 20 ml heparin blood/ 5 ml heparin bone marrow for MRD/biological studies, see 9.2.2

9.8 Evaluation at progression

Any progression should be documented according to the following investigations:

- Physical examination, including disease related symptoms
- CT of involved nodal areas, especially assessment of measurable lesions
- Bone marrow biopsy, cytology with immunophenotyping (optional)
- Clinical laboratory examination:
  - CBC with differential and platelet count;
  - Immunophenotyping (double staining CD19/CD20/CD5)
  - sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH
- Optional human anti-murine antibodies (HAMA; only rituximab maintenance arm)
- 20 ml EDTA blood / 5 ml EDTA bone marrow and 20 ml heparin blood/ 5 ml heparin bone marrow for MRD/biological studies, see 9.2.2

9.9 Duration of follow-up

Patients in CR/PR will be followed every 2 months during the maintenance therapy. All patients off study (irrespective or the reason) will be followed until death.

9.10 Time schedule of diagnostic procedures (baseline and follow-up)

Examination	Base-line	Before each cycle	After 3.R-FC or 4.R-CHOP	After chemo-therapy	Every 2 months	Every 6 months	At progression
Inclusion/exclusion criteria, informed consent	X			X			
Medical history, demographics, current medical condition	X						
Physical examination including vital signs, performance status	X[1]	X	X	X	X	X	X
ECG/echocardiography	X			X[2]			
Chest X-ray	X			X[2]			
CT scan[3]	X		X	X		X	X
Bone marrow biopsy	X		X[4]	X[4]		X[4]	X
Laboratory tests[5]	X[1]	X	X	X	X	X	X
Direct Coombs test	X						
Anti-HIV, HBV, HCV	X						
Urine analysis[6]	X						
Flow cytometry[7]	X			X		X	X
Biological program/MRD	X Blood, BM			X Blood, BM	X Blood only	X Blood, BM	X Blood, BM
Concomitant medication	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	

1 Within 14 days prior to the first administration of therapy.

2 Additionally repeated as clinically indicated.

3 All tumour lesions at baseline, follow target lesions accordingly

4 Only as confirmation of complete response (histology).

5 CBC with differential and platelet count. Sodium, potassium, creatinine, ASAT, ALAT, alkaline phosphatase, γ-GT, bilirubin, LDH.
Additionally at baseline: Glucose, BUN, uric acid, total protein, albumin, IgG, IgM and IgA.

6 pH-value, erythrocytes, total protein, glucose (dipstick).

7 Quantitative determination of circulating (normal) B-lymphocytes and/or MCL cells (e.g. CD19/20/CD5 double staining)

10. Toxicities

10.1 Adverse events

Special attention has to be paid to the occurrence of adverse events (AE) throughout every stage of the study. Investigators should be familiar with adverse events that have been previously observed in association with rituximab, the chemotherapy applied and IFN-alpha. All observed toxicities should be graded according to the CTC-criteria (appendix B) and documented in the CRFs

10.2 Serious adverse events

A serious adverse event (SAE) is defined as any observed medical condition that:

- results in death, or
- is life-threatening, or
- results in persistent or significant disability/incapacity.

Any serious adverse event has to be reported within 48 hours to the study centre and thereafter documented in detail as indicated on the enclosed SAE form (in addition to the regular CRF form). The following information is required:

- Date and time of onset.
- Duration (date of onset and end).
- Peak intensity [according to CTC criteria, [appendix B].
- Drug relationship of the AE to the investigational product (for definitions, see below).
- Outcome of the adverse event (recovered completely / with residual effects, continuing).
- Assessment of the seriousness of the event.

The investigator has to classify the drug relationship of an SAE according to the following definitions:

None: The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/ worsening of the adverse event exists.

Unlikely: The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug provide no indication of involvement in the occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/ worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug, but another cause is much more probable and/or another cause is confirmed and involvement of the study drug in the occurrence/ worsening of the adverse event is unlikely.

Possible: Regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the pharmacological properties of the study drug, but another cause is just as likely to be involved or although the pharmacological properties of the study drug provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause can be identified.

Probable: The pharmacological properties of the study drug and the course of the adverse event (after rechallenge) and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.

Definite: The pharmacological properties of the study drug and the course of the adverse event (after rechallenge) and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event, and no other cause exists.

11. Reasons for going off protocol

In the case record form the reason for going off protocol should be documented according to the following listing:

- Progressive disease.
- Adverse event.
- Concomitant disease.
- Death.
- Other reason.

12. Causes of death

In the case record form, the cause of death should be documented according to the following listing:

- Mantle cell lymphoma.
- Complication of therapy.
- Intercurrent disease.
- Secondary malignancy.
- Other cause.

13. Criteria of evaluation

13.1 Response criteria

Response to treatment will be evaluated after the end of chemotherapy and at relapse. Evaluation of response will be done according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. The following criteria are considered anatomic definitions (Table 1). In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

1. CR requires the following:

- Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalisation of those biochemical abnormalities (e.g. lactate dehydrogenase (LDH]) definitely assignable to NHL.
- 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).
- 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. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (>20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

2. **CR/unconfirmed (CRu)** includes those patients who fulfil criteria 1 and 3 above, but with one or more of the following features:

- A residual lymph node mass greater than 1.5 cm 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).

3. PR 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:
  - they should be clearly measurable in at least two perpendicular dimensions,
  - they should be from as completed disparate regions of the body as possible, and
  - 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.
- Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report and preferably confirmed by immunohistochemistry.
- No new sites of disease.

4. Stable disease/No change (NC) is defined as less than a PR (see above) but is not progressive disease (see below).

5. Relapsed disease (RE) (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.

6. Progressive disease (PD) (after PR, non-responders) requires the following:

- 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
- Appearance of any new lesion during or at the end of therapy

13.2 Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria. PET scanning is until know not accepted as the sole instrument for response measurements.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 4 weeks after the end of treatment to assess response.
2. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Table 1. Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal/indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/progression	Enlarg.liver/spleen/new sites	New/increased	New/increased	Reappearance

NOTE. See text for definitions of 'normal' and 'indeterminate.'

In case of relapse after initial complete remission the following information will be registered:

- Date of relapse.
- Site of relapse.
- Whether there is histological or cytological confirmation of the relapse.

14. Forms and procedures for collecting data

14.1 CRF's and schedule for completion

part no.	Title
1	Registration forms (randomization)
2	Induction chemotherapy (tumor measurements, chemotherapy cycles 1-8 (R-CHOP) or 1-6 (R-FC), response evaluation, side effects), report of death
3	Randomization of maintenance form
4	Maintenance and follow-up forms in first CR, CRu or PR, report of death
5	SAE form
6	Molecular diagnostics form

15. Statistical methods

The aim of this study is to answer the following independent questions in the treatment of mantle cell lymphomas:

- Can R-FC improve the reduction of lymphoma mass compared to R-CHOP and so become a new standard for initial cytoreductive therapy?
- Can maintenance with rituximab substitute the interferon maintenance and even improve the progression free survival in patients after successful initial cytoreductive therapy?

15.1 Parameters for the comparison of R-FC and R-CHOP

The parameter for the comparison of R-FC and R-CHOP will be the percentage of complete remissions after initial cytoreductive therapy. According to the known results of R-FC and R-CHOP in lymphoma therapy, a relevant difference between R-CHOP and R-FC in the overall response rates is not expected. For both therapies an overall response rate of about 90% is expected. Since it is well known that the prognosis of patients who do not reach at least a PR in the initial therapy is very poor, it will be also necessary to control this parameter during the study. If an unexpected relevant difference in the overall response rates is observed during the study, the initial randomisation should be stopped and all patients should be assigned to the superior therapy. In this case the CR rates will not be important for the choice of the initial therapy. If no relevant differences in the overall response rates are observed, a one sided Fisher test will be performed at the end of the recruitment to test whether the rate of CR's after R-FC is significantly improved compared to R-CHOP. The statistical parameters for controlling the overall response rates and for testing the CR rates are chosen in the following way:

The working significance level for all statistical evaluations in this part of the study will be set to alpha=0.05.

The expected CR rate after R-CHOP is according to the observations about 50%; a clinical relevant improvement by R-FC would be a CR rate of 65%. Such an improvement should be detected by the one sided Fisher test with a power of about

95%. According to these parameters about 246 observations for each treatment would be necessary.

To control the overall response rates, a difference of 85% to 95% will be clinically so relevant that initial randomisation should be terminated with a probability of about 95%. Overall response rates will be controlled by a restricted sequential procedure[26,27] in the following way:

For sequential monitoring of the study the statistics V and Z will be calculated with the following formulae every time when new data are available:

$$Z_k = \frac{n_k S_{m_k} - m_k T_{n_k}}{m_k + n_k} \qquad V_k = \frac{m_k n_k (S_{m_k} + T_{n_k})((m_k - S_{m_k}) + (n_k - T_{n_k}))}{(m_k + n_k)^3}$$

n_k := number of evaluable patients after R-CHOP at the k-th analysis

m_k := number of evaluable patients after R-FC at the k-th analysis

T_{m_k} := number of evaluable patients graded CR, CRu or PR after R-CHOP at the k-th analysis

S_{m_k} := number of evaluable patients graded CR, CRu or PR after R-FC at the k-th analysis

Stopping rule:

The continuation region is defined as

$$Z_{i+1} \in (-a - \lambda V_{i+1} + \kappa_{i+1}, a + \lambda V_{i+1} - \kappa_{i+1}) \wedge V_{i+1} < L$$

with a = 3.518, λ = 0.4987, L=11.02 and the correction for discrete monitoring:

$$0 =: V_0 < \mathrm{K} < V_i < V_{i+1}: \qquad \kappa_{i+1} = 0.583\sqrt{V_{i+1} - V_i}$$

For $Z_{i+1} \geq (a + \lambda V_{i+1}) - \kappa_{i+1}$ the null hypothesis will be rejected and R-FC is found to be significantly superior, while

for $Z_{i+1} \leq (-a - \lambda V_{i+1}) + \kappa_{i+1}$ the null hypothesis will be rejected and R-CHOP is found to be significantly superior.

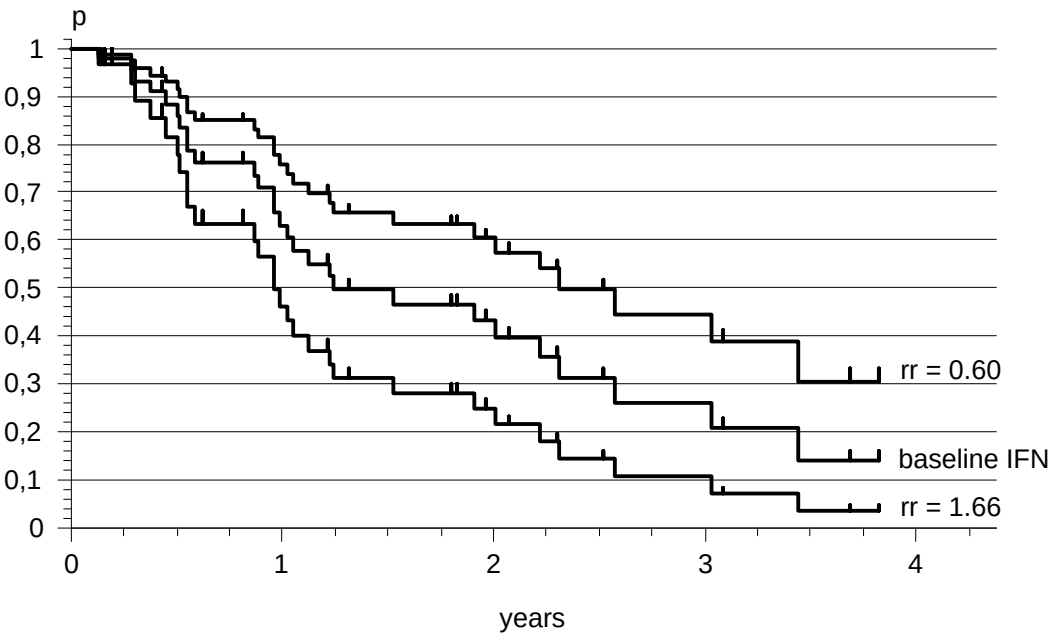
For $V_{i+1} \geq L \wedge \forall j < i+1\, Z_j \in (-a - \lambda V_j + \kappa_j, a + \lambda V_j - \kappa_j)$ the null hypothesis will be accepted.

15.2 Recruitment necessary for the comparison of R-FC and R-CHOP

The expected rates for randomisations per year were estimated by the number of patients that were submitted to the former European mantle cell study. The following minimal randomisation rates will be attainable in the study:

Germany GLSG	35 / year
Germany OSHO	15 / year
France	15 / year
Swiss, Italy, Spain	5 / year
HOVON	5 / year
Nordic LG	5/ year
Netherlands	15 / year
total:	**95 / year**

The rate of patients, that had to be excluded because of wrong histology in the European mantle cell study was about 9%; the compliance in the German study comparing R-CHOP with CHOP was very well for R-CHOP in the group of mantle cell lymphomas, without premature discontinuations of therapy. Therefore, the rate of randomised patients that would not be evaluable should be about 10%; this results in an expected recruitment time (under the assumption that there is no relevant difference in the overall response rates) of about 6 years.



15.3 Parameters for the comparison of maintenance with rituximab and maintenance with interferon

Using the data of the interferon group in the former European mantle cell study as baseline in a proportional hazard model, the improvement expected by the new maintenance with rituximab can be expressed by reduction of relative risk (*rr*).

Since a risk reduction to 60% was observed for indolent lymphomas by interferon maintenance, this seems to be a clinical relevant improvement for the new therapy. Providing a continuous entry of patients into the study, the number of observed events will be a function of the recruitment rate, the observation time and the improvement reached by rituximab maintenance. Using the described baseline observations the following estimates for the percentage of observed events are obtained.

Years of recruitment		***rr* for rituximab maintenance**					
	IFN	**1.66**	**1.29**	**0.88**	**0.77**	**0.68**	**0.6**
1	17%	25%	21%	15%	14%	12%	11%
2	32%	44%	38%	29%	26%	24%	22%
3	45%	58%	52%	41%	38%	35%	32%
4	54%	67%	61%	51%	47%	44%	40%
5	61%	73%	67%	57%	53%	50%	46%
6	65%	77%	71%	61%	57%	54%	50%
7	68%	80%	74%	64%	60%	57%	53%
8	70%	82%	77%	66%	63%	59%	55%
9	72%	83%	78%	68%	64%	60%	56%
10	73%	85%	80%	70%	66%	62%	58%

According to the recruitment for initial therapy, about 77 patients per year in CR or PR will be available for the second randomisation; expecting that about 10% of the patients will refuse the second randomisation, a recruitment of 70 patients per year is expected. Providing a balanced distribution between the two therapy arms, the expected numbers of events in both arms can be calculated:

Years of recruitment	*rr* for rituximab maintenance						
	1.66	**1.29**	**1.0**	**0.88**	**0.77**	**0.68**	**0.6**
1	15	13	12	11	11	10	10
2	54	49	45	43	41	39	38
3	108	101	94	90	87	83	80
4	170	161	152	147	142	137	132
5	234	224	212	206	199	193	187
6	298	286	272	265	257	249	241
7	361	348	333	324	314	305	295
8	425	411	393	383	371	361	350
9	489	473	453	441	429	417	404
10	553	535	513	500	486	472	458

For a working significance level alpha=0.05 and a power of 95% the number of events (relapse or death) necessary for a two sided fixed sample trial is about 200.

For ethical and scientific reasons it will be necessary to do this trial with planned interim analyses. The most effective way for planned interim analyses is a sequential procedure[26;27]. The statistics Z and V will be calculated every time when new data with reported events are available:

$$Z = n - \sum_{i=1}^{k} o_i \left(\frac{r_{i\,/\,IFN}}{r_i}\right) \qquad V = \sum_{\{i:r_i>1\}} \frac{o_i(r_i - o_i)}{(r_i - 1)} \frac{r_{i\,/\,rituximab}}{r_i} \frac{r_{i\,/\,IFN}}{r_i}$$

$d_1 < d_2 < \ldots < d_k$: *sequenz of values of observed uncensored progression free times*

o_i:= *number of observed uncensored progression free times* $= d_i$

r_i:= *number of observed progression free times* $\geq d_i$

n:= *number of observed events in the IFN – group*

$r_{i/\,IFN}$:= *number of observed progression free times* $\geq d_i$ *in the IFN – group*

$r_{i/\,rituximab}$:= *number of observed progressionfree times* $\geq d_i$ *in the Rituximab – group*

Stopping rule:

The continuation region is defined as

$$Z_{i+1} \in \left(-a - \lambda V_{i+1} + \kappa_{i+1}, a + \lambda V_{i+1} - \kappa_{i+1}\right) \wedge V_{i+1} < L$$

with *a* = 8.899, λ = 0.1918, L = 60 and the correction for discrete monitoring:

$0 =: V_0 < \mathrm{K} < V_i < V_{i+1}:$ $\qquad \kappa_{i+1} = 0.583\sqrt{V_{i+1} - V_i}$

For $Z_{i+1} \geq (a + \lambda V_{i+1}) - \kappa_{i+1}$ the null hypothesis will be rejected and rituximab maintenance is found to be significantly superior, while

for $Z_{i+1} \leq (-a - \lambda V_{i+1}) + \kappa_{i+1}$ the null hypothesis will be rejected and interferon maintenance is found to be significantly superior.

For $V_{i+1} \geq L \wedge \forall j < i+1\, Z_j \in (-a - \lambda V_j + \kappa_j, a + \lambda V_j - \kappa_j)$ the null hypothesis will be accepted.

The sample size until termination of this procedure depends on observed results and will grow to a maximum value under the null hypothesis (*rr* = 1.0). The following values can be calculated for the procedure, a continuous balanced randomisation of 70 patients per year provided:

Parameter	number of events	Estimated duration of recruitment
median number of events at termination for *rr* = 1.0 (no improvement)	240	6 years
median number of events at termination for *rr* = 0.60	96	3.5 years
median number of events at termination for *rr* = 0.77	240	6 years
median number of events at termination for rr = 1.66 (disimprovement by rituximab, improvement by interferon lost)	96	3 years
p90 for *rr* = 0.60	197	5 – 5.5 years
p90 for *rr* = 1.66	197	4.5 years
possible maximum:	240	6 years

15.4 Expected number of treatments in this trial

According to the sequential design of the trial, the number of treatments is dependent

on the results observed during the monitoring; the following table shows the maximum numbers expected in the trial:

patients treated with R-CHOP:	285
patients treated with R-FC:	285
patients treated with IFN-maintenance:	220
patients treated with rituximab-maintenance:	220

15.5 Evaluable patients to compare treatment results for initial cytoreductive therapy

15.5.1 Success, failure and premature discontinuation of initial cytoreductive therapy

All patients who start the initial cytoreductive therapy according to the protocol will be evaluated for response to therapy. The response to treatment is always evaluated in comparison to the status before start of therapy. Death during therapy or within four weeks after therapy is always graded as treatment failure, even if a partial or complete remission was achieved before. Progression of the lymphoma during therapy after at least one course of therapy is graded as treatment failure if the therapy is stopped. Patients at the end of therapy who have only a stable disease (no change) after at least 3 courses of R-FC or 4 courses of R-CHOP are also graded as treatment failure. Patients who achieve a CR, CRu or PR at the end of therapy after at least 6 courses of R-CHOP or 4 courses of R-FC are graded as success of therapy. Patients who discontinue therapy without progression of the lymphoma with less than 3 courses of R-FC or 4 courses of R-CHOP are graded as "premature discontinuation" of therapy. Patients who achieve a CR, CRu or PR at the end of therapy are also graded as "premature discontinuation" of therapy, if they received less than 6 courses of R-CHOP or 4 courses of R-FC.

15.5.2 Evaluable patients for the statistical monitoring of the overall response rate

All randomised patients with mantle cell lymphoma who finish the initial therapy

according to the randomisation result with success or failure are evaluated for the overall response rate. Patients who do not have a mantle cell lymphoma (according to reference histology), who do not start the treatment or start with another treatment than randomised, or prematurely discontinue therapy are excluded from this evaluation.

15.5.3 Evaluable patients for the CR-rates of initial cytoreductive therapy

All randomised patients that are evaluable for the statistical monitoring of the overall response rate will be evaluated for the CR-rate of the initial cytoreductive therapy, if after evaluation for the overall response rates of 246 evaluable patients in each treatment arm, no significant differences were found. For the statistical calculations here, only patients with "classical CR" will be graded as CR; patients with PR, NC and patients who die during initial therapy will be graded as not successful in achieving a CR by the initial cytoreductive therapy. For statistical calculations, patients in CRu will be included in the PR group.

15.6 Evaluable patients to compare interferon-maintenance with rituximab-maintenance

15.6.1 Parameter for evaluation of interferon-maintenance and rituximab-maintenance

To compare the effect of maintenance therapy for patients after successful initial cytoreductive therapy, the progression free survival after the end of the initial therapy will be evaluated. The progression free survival after the end of initial therapy is defined as the time interval between the last day of the last cycle of initial therapy and the date of disease progression or death, whichever comes first. If no event has been observed at an evaluation, the patient is censored at the date of the last follow up examination. Patients will only be evaluated for this parameter, if there is a sufficient documentation for the initial therapy. Patients who change the maintenance therapy without documented progression or patients who start another antineoplastic therapy without progression of the lymphoma or a new hematological or oncological disease will be censored at the time of protocol violation. Dose reduction or discontinuation of maintenance therapy will not be a reason for censoring.

15.6.2 Evaluable patients for the statistical monitoring of interferon-maintenance versus rituximab-maintenance

All patients with a mantle cell lymphoma and successful initial therapy who are randomised for maintenance with interferon versus maintenance with rituximab and who start the therapy according to the randomisation result will be evaluated for the statistical monitoring of progression free survival after end of initial therapy. Patients who do not have a mantle cell lymphoma (according to reference histology), who do not start the treatment or start with an other treatment than randomised will be excluded for this evaluation.

15.7 Evaluation during the Trial

Data about recruitment and pooled data for all treatments about response to initial therapy, progression free survival after start and end of initial therapy and overall survival will be evaluated every six months and reported to the study chairman and co-chairmen. Toxicity will be also reported every six months in all treatment arms including all patients who started any protocol treatment, according to the treatment actually taken. These data will also be reported at the meetings of the study group and may also be reported (only if approved by the study chairman and co-chairman, and without any disclosure of the randomised arms) at conferences. Beside toxicity data no other data for the comparison of R-FC, R-CHOP, interferon-maintenance and rituximab-maintenance will be disclosed before the decision of the according sequential procedure.

15.8 Parameters for final and interim reports

Beside the main parameters success of initial therapy, CR after initial therapy and progression free survival after initial therapy, the following parameters will also be evaluated for final and interim reports in this study:

- last response to initial therapy: last evaluable response to initial therapy after receiving at least one course of therapy.
- survival after registration / first randomisation / second randomisation: time from

registration / first randomisation / second randomisation in this study until death; if the patient is still alive, the patient is censored at the date of last contact.

- survival after start / end of initial therapy: time from start / end of initial therapy in this study until death; if the patient is still alive, the patient is censored at the date of last contact.
- progression free survival after registration / first randomisation / second randomisation: time from registration / first randomisation / second randomisation in this study until death or progression of the lymphoma; if no event has been observed at an evaluation, the patient is censored at the date of the last follow up examination.
- time to treatment failure after start of initial therapy: time from start of initial therapy until first failure; a failure will be defined as failure of initial therapy or progression of the lymphoma or death of the patient; patients who premature discontinue therapy will be censored at discontinuation of therapy.

15.9 Final and interim reports about R-CHOP and R-FC

The first interim report for the comparison of R-FC and R-CHOP will be done if the monitoring for the overall response rate has shown a significant improvement or after observation of at least 246 treatments for each therapy. If a significant improvement is observed, all patients in this study will be assigned to the superior treatment; otherwise the standard therapy with R-CHOP will be assigned to all further recruited patients. Results will be disclosed to the study group after all randomised patients have finished the initial therapy.

In the final and interim reports comparing R-CHOP and R-FC the following parameters and groups will also be evaluated to provide comparable parameters to other studies:

- last response to initial therapy for all registered and all randomised patients
- survival after registration and after first randomisation for all registered and all randomised patients
- survival after start of initial therapy for all registered and all randomised patients
- progression free survival after registration and after first randomisation for all registered and all randomised patients
- time to treatment failure after start of initial therapy for all registered and all

randomised patients

All reports will contain a "strict intention to treat analysis" (evaluated as randomised) and an analysis according to real given treatment.

15.10 Final and interim reports for rituximab-maintenance vs. interferon maintenance

The first interim report for the comparison of rituximab-maintenance and interferon maintenance will be done if the sequential procedure monitoring the progression free survival after end of initial therapy has accepted or rejected the null hypothesis. At this point the results will be disclosed to the study group and the second randomisation will be stopped.

In the final and interim reports about maintenance therapy the following parameters and groups will also be evaluated to provide comparable parameters to other studies:

- survival after second randomisation for all randomised patients
- survival after start and end of initial therapy for all randomised patients
- progression free survival after second randomisation for all randomised patients

All reports will contain a "strict intention to treat analysis" (evaluated as randomised) and an analysis according to real started treatment.

15.11 Randomisation

After verification of eligibility (registration checklist) patient randomisation will be performed preferably centrally at the data center in Munich or, alternatively, by the local data center as defined by the national study group listed in 6.3 (see table below); in the latter case, the registration form and the result of the randomization will be subsequently forwarded to the central data center in Munich by fax. All groups participating in this trial have to decide whether the randomization should be performed centrally at the data center in Munich or by the local data center of the national study group. Both sequential randomization procedures will be done with an allocation ratio of 0.5 applying the method of random permutated blocks as described [27]. If the randomization procedure is performed at the local data center of the participating study group, the local data center has to define a procedure to use permutated blocks for allocation of patients.

Centers not associated to one of the participating study groups will perform the randomization at the central data center in Munich. Registration is only accepted from authorised investigators and must be done before the start of the treatment.

Group	phone	fax	Internet http://
Germany GLSG	+44-89-699583-0	+44-89-699583-12	-
HOVON	+31-10-4391568	+31-10-4391028	www.hdc.hovon.nl/top
Nordic LG	+45-35-451146	+45-35-454841	
France GELA			

A list of questions to be answered during both randomisation procedures is included in the registration checklist, which is part of the case report forms. The checklist should be completed by the responsible investigator before the patient is randomised.

15.11.1 Randomisation 1 (choice of initial chemotherapy)

For the first randomisation the following data must be provided (see registration form):

- Institution number assigned to the responsible investigator
- Name, phone and fax number of the person requesting the randomisation
- Name of the responsible investigator
- Patient's initials (at least 2 letters)
- Patient's birth date (day/month/year)
- Name, address and journal-number/entry-number of the local pathology
- Eligibility criteria
- Stratification criteria

After checking the eligibility criteria, a number will be allocated to the patient (patient sequential identification number at the institution). This number and the randomisation result will be recorded on the registration checklist and sent back by fax to the person requesting the randomisation and to the responsible investigator. The sequential identification number in combination with the institution number identifies the patient and must be reported on all case report forms.

If the first randomisation was stopped but recruitment for the study has not been finished, all patients should be registered before start of initial therapy using the randomisation form for the first randomisation.

15.11.2 Randomisation 2 (choice of maintenance therapy)

All patients with response to the initial cytoreductive therapy may be randomised for interferon maintenance versus rituximab maintenance. For the second randomisation the following data must be provided on the randomisation checklist:

- Institution number assigned to the responsible investigator
- Name, phone and fax number of the person requesting the randomisation and name of the responsible investigator
- Patient sequential identification number at the institution assigned at first randomisation/registration
- Eligibility criteria
- Stratification criteria

The randomisation result will be recorded on the randomisation checklist and send back by fax to the person requesting the randomisation and to the responsible investigator.

15.12 Statistical design

Randomisation will be stratified according to the factors listed in chapter 6.3. Statistical analyses will be conducted at the data centre of the European MCL Network. All randomised patients will be included in the analyses according to treatment allocated at randomisation. The two arms of Progression Free Survival (DFS) and Overall Survival (OS) will be compared using a two-sided logrank test (Mantel 1966) at 0.05 level of significance. Survival curves will be estimated with the Kaplan-Meier technique. To adjust for confounding variables the Cox proportional hazard model (Cox 1972) with retrospective stratification will be used. Response to Treatment will be compared by the Chi-square test (responders versus no responders) at 0.05 level of significance. Toxicity will be reported in the two treatment arms including all patients who started any protocol treatment, according to the treatment actually taken.

16. Ethical Considerations

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edingburgh Amendment 2000) and the ICH-GCP Guidelines of 17 January 1997. Prior to its activation, the study must be approved by the local ethic committees. Especially, each patient will be informed about the nature and purpose of the study, the expected duration and the potential benefits / risks of participation. Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision. (See appendix D for votes of the local ethic committees.)

16.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

16.2 Patient information and consent

Written Informed consent of patients is required before registration. The procedure and the risks and the opinions for first-line therapy in MCL will be explained to the patient in a written form (see appendix). The information for the patients will be prepared by the participating groups in the national language of the patient.

17. Trial insurance

According to the local regulations for each country, an insurance for patients treated in this trial will be necessary. The necessary regulations for the insurance in this study will be done by the participating groups. Appendix C contains the necessary information about insurance for this study.

18. Publication policy

The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the Data Centre of the European MCL Network in Munich. A draft manuscript will be submitted to the Data Centre and all co-authors for review. After revision by the Data Centre and the other co-authors, the manuscript will be sent to a peer reviewed scientific journal. Authors of the manuscript will include the study co-ordinator(s), the lead investigators of the major groups, investigators who have included more than 10% of the evaluable patients in the trial (by order of inclusion), the statistician, and others who have made significant scientific contributions. Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomised treatment arms may be made publicly available before the recruitment is discontinued. Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered in the trial, or any subgroup of the trial patients. Such a publication cannot include an analysis of any of the study end-points unless the final results of the trial have already been published.

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20. ABBREVIATIONS

AE	Adverse event
ALAT (SGPT)	Alanine aminotransferase
ASAT (SGOT)	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CNS	Central nervous system
CR	Complete response
CRF	Case report form
Cru	Complete response/unconfirmed
CTC	Common toxicity criteria
ECG	Electrocardiogram
ENT	Ear, Nose and Throat
GCP	Good Clinical Practice
GMP	Good Manufacturing Process
HAMA	Human anti-murine antibodies
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IV	Intravenous
MM	Millimol
PBS	Phosphate buffered saline
PD	Progressive disease
PFS	Progression-free-survival
PPD	Product of two largest perpendicular diameters
PR	Partial response
PS	Performance status
SPD	Sum of the products of the greatest diameters
SAE	Serious adverse event
ULN	Upper limits of normal

APPENDIX A: WHO PERFORMANCE CRITERIA

Definition	Grade
The patient is able to carry out all normal activities without restriction	0
The patient is restricted in physically strenuous activity but able to carry out light work, patient is ambulatory	1
Patient is ambulatory and capable of all self-care but unable to carry out any work, patient is out of bed more than 50% of waking hours	2
Patient is capable of only limited self-care and confined to bed or chair more than 50% of waking hours	3
Patient is completely disabled; cannot carry out any self-care and is totally confined to bed or chair	4

Appendix B: Common toxicity criteria (CTC) V.2.0

COMMON TOXICITY CRITERIA (NCI CTC)

Grade Toxicity	0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤ 18 years)	90% cellularity average				

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
younger adults (19-59) older adults (≥ 60 years) Note: Grade Bone marrow cellularity only for changes related to treatment not disease.	60-70% cellularity average 50% cellularity average				
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
For BMT:	none	≤2 u pRBC (≤*15cc/kg*) in 24 hours elective or planned	3 u pRBC (>*15* ≤*30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (>*30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac- ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with <u>no</u> bleeding	laboratory findings <u>and</u> bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					

Grade Toxicity	0	1	2	3	4
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Dermatology/Skin-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting Also consider Dehydration.	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion-pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.	absent	-	-	present	-
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical) Note: Documented viral hepatitis is graded in the INFECTION category.	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration- anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine *Note: Adjust to age-appropriate levels for pediatric patients.*	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Secondary Malignancy-Other (Specify type, _____) excludes metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

APPENDIX C: CERTIFICATE OF INSURANCE

Gothaer
Versicherungen

Partner im Parion-Verbund

Hauptverwaltung
Abteilung KF-HKM 11

Gothaer Allee 1
50969 Köln

Gothaer Allgemeine Versicherung AG · 50598 Köln

Deutsche Krebsgesellschaft e.V.
z. Hd. Frau Inga Rossion
Steinlestr. 6

60596 Frankfurt

Köln, 15.12.2003

Versicherungsbestätigung zur
Probandenversicherung Nr. 37.907.546060 (bisher: 11.444.546060)

Sehr geehrte Damen und Herren,

zur Vorlage beim Bundesinstitut für Arzneimittel und Medizinprodukte, bei der Ethikkommission und den mit den klinischen Prüfungen beauftragten Personen/Ärzten bzw. Krankenanstalten bestätigen wir Ihnen das Bestehen einer Probandenversicherung für die Zeit vom 01.01.2004 bis 01.01.2005.

Während dieser Zeit sind alle Studien, die begonnen werden und die noch andauern – auch über diesen Zeitraum hinaus – automatisch vom Versicherungsschutz erfaßt. Die Höchstleistung beträgt für alle Versicherungsfälle aus den klinischen Prüfungen

5.113.000 EUR, wenn bis zu 1.000 Personen,
10.226.000 EUR, wenn mehr als 1.000 Personen bis zu 3.000 Personen,
15.339.000 EUR, wenn mehr als 3.000 Personen

an den klinischen Prüfungen teilnehmen. Die Versicherungsleistungen für die einzelnen versicherten Personen ermäßigen sich im entsprechenden Verhältnis, wenn die Summe der einzelnen Versicherungsleistungen diesen Höchstbetrag überschreiten würde.
Die Höchstleistung je versicherte Person beträgt 512.000 EUR.

Versicherungsschutz besteht für Gesundheitsschädigungen, die bis spätestens 5 Jahre nach Abschluß der beim Versicherten durchgeführten klinischen Prüfung eingetreten sind und nicht später als 10 Jahre nach Beendigung der klinischen Prüfung dem Versicherer gemeldet werden. Für den Vertragsumfang gelten die

Allgemeinen Versicherungsbedingungen für klinische Prüfungen von Arzneimitteln (Probandenversicherung / Arzneimittel)

Mit freundlichen Grüßen

i. V. i. A.

Gesellschaft: Gothaer Allgemeine Versicherung AG, Köln
Vorstand: Dr. Werner Görg (Vorsitzender)
Dr. Reinhard Blei, Manfred Rupprecht, Helmut Söhler, Dr. Herbert Schmitz
Aufsichtsrat/Rechtsform: Dr. Roland Schulz (Vorsitzender)/Aktiengesellschaft, Sitz Köln, Registergericht AG Köln, HRB 35474

APPENDIX D: POSITIVE VOTUM OF THE ETHICS COMMITTEE

Ethikkommission der Medizinischen Fakultät
der Ludwig-Maximilians Universität
Vorsitzender: Prof. Dr. Gustav Paumgartner

Ludwig
Maximilians
Universität
München

Marchioninistr. 15
81377 München
Tel: (089) 7095 4609
Fax: (089) 7095 7609
e-mail: Ethikkommission@
med2.med.uni-muenchen.de
30.07.2003

Klinikum der Universität München – Großhadern
Marchioninistr. 15 81377 München

Herrn
Prof. Dr. W. Hiddemann
Med. Klinik III
Klinikum Großhadern

- im Hause –

EINGEGANGEN
am 31. Jul. 2003

Projekt Nr. 149/03

Wirksamkeit einer Rituximab- Erhaltungstherapie nach Induktions-Immunochemotherapie (R-CHOP vs. R-FC) für ältere Patienten mit Mantelzell-lymphom, die nicht für eine autologe Stammzell- Transplantation geeignet sind

Sehr geehrter, lieber Herr Kollege Hiddemann,
sehr geehrter Herr Kollege Dreyling,

besten Dank für Ihr Schreiben vom 16.07.2003 mit der Beantwortung unserer Fragen bzw. Erfüllung von Auflagen und noch ausstehenden bzw. überarbeiteten Unterlagen (Patienteninformation).

Die Ethikkommission (EK) kann Ihre Studie die ethisch-rechtliche Unbedenklichkeit zuerkennen, sobald Sie, wie angekündigt, die Versicherungspolice nachreichen und die entsprechenden Angaben zur Versicherung in die Patienteninformation einfügen.

Die EK geht davon aus, dass Sie die klinische Prüfung gemäß §67(1) AMG bei der Regierung von Oberbayern anzeigen werden.

Vorsorglich möchte ich darauf hinweisen, dass auch bei einer positiven Beurteilung des Vorhabens durch die EK die ärztliche und juristische Verantwortung für die Durchführung des Projektes uneingeschränkt bei Ihnen und Ihren Mitarbeitern verbleibt.

Sie werden gebeten, die EK über alle schwerwiegenden oder unerwarteten Ereignisse im Rahmen der Studie zu unterrichten.

Änderungen des Studienprotokolls sind der EK mitzuteilen.

Mit freundlichen Grüßen

Prof. Dr. G. Paumgartner
Vorsitzender der Ethikkommission

Appendix E: Registration Form

Version: October 29, 2004

Efficacy of maintenance therapy with rituximab after induction therapy (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for autologous stem cell transplantation

A European Intergroup Trial
of the
German Low Grade Lymphoma Study Group
GELA
HOVON
Nordic Lymphoma Group

MCL elderly/ HOVON 55MCL	**REGISTRATION** **EUROPEAN MCL - STUDY** **for elderly patients**
	Contents: 4 Registration forms

Please register patient via:

Internet through TOP or
send this form by fax or report by telephone to
HOVON Data Center

Internet: www.hdc.hovon.nl/top
Fax: +31.10.4391028
Tel: +31.10.4391568

And send to:

HOVON Data Center
Erasmus MC – Daniel den Hoed
P.O.Box 5201
3008 AE ROTTERDAM
The Netherlands

Patient initials: ⌊_⌊_⌊_⌋

MCL elderly/HOVON 55 MCL Efficacy of maintenance therapy after induction (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for autologous stem cell transplantation **Fax: +31.10.4391028**	**Form 01 / 04** ***registration form***

THE PATIENT CONSENT MUST BE GIVEN BEFORE TREATMENT IS STARTED!

Date of informed consent: ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌋ (dd.mm.yy)

CLINICAL INSTITUTION

Clinic-No.: 4 9 4 Hospital name: ……

Physician: .....

Phone (physician): ..... Fax: .....

Study nurse: .....

Phone (study nurse): ..... Fax: .....

PATIENT DATA

Initials surname / first name: ⌊_⌋/⌊_⌋ Patient-No.: ⌊_⌊_⌊_⌋

Date of initial diagnosis: ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌋ (dd.mm.yy)

Date of birth: ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌋ (dd.mm.yy) Sex: ❍ female ❍ male

Histology of initial diagnosis: ....

The diagnosis of a mantle cell lymphoma must be histologically confirmed before inclusion in this study!

DATA OF THE STUDY-GROUP

❍ GELA

❍ GLSG (German Lymphoma Study-Group)

❍ HOVON

❍ Nordic Lymphoma Group

❍ other centers: .....

Clinic: ..... Signature: .....Date: ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌋

Patient initials: ⌊ ⌋⌊ ⌋⌊ ⌋

MCL elderly/HOVON 55 MCL Efficacy of maintenance therapy after induction (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for autologous stem cell transplantation **Fax: +31.10.4391028**	**Form 02 / 04** ***registration form***

Clinic-No.: 4 9 4 Patient-No.: ⌊ ⌋⌊ ⌋⌊ ⌋ Date of birth: ⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋

Pathologic Institute (local pathologist):

Date of biopsy: ⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋ Date of histology: ⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋ (dd.mm.yy)

Registration-No. (local): ..... *(this information is mandatory!)*

Institute: .....

Street: .....

Zip Code: ..... City: .....

Diagnosis: ❍ MCL

Review pathologist:

❍	Feller	Lübeck	Germany	❍	Campo	Barcelona	Spain
❍	Hansmann	Frankfurt/M.	Germany	❍	Kluin	Groningen	Netherlands
❍	Möller	Ulm	Germany	❍	Kodet	Prague	Czech Republic
❍	Müller-Hermelink	Würzburg	Germany	❍	Pedrinis	Locarno	Switzerland
				❍	Pileri	Bologna	Italy
❍	Parwaresch	Kiel	Germany	❍	Ralfkiaer	Copenhagen	Denmark
❍	Stein	Berlin	Germany	❍	van Krieken	Nijmwegen	Netherlands
❍	Berger	Lyon	France	❍	Wolf-Peeters	Leuven	Belgium
❍	Brousse	Paris	France				

Registration No. *(if known):* .....

B-SYMPTOMS AND INTERNATIONAL PROGNOSTIC INDEX (IPI)

loss of weight (> 10 % within 6 months) ..... yes ❍ no ❍
night sweat ..... yes ❍ no ❍
fever > 38 °C ..... yes ❍ no ❍

Stage: ❍ II ❍ III ❍ IV
Extranodal involvement: bone marrow yes ❍ no ❍
liver yes ❍ no ❍
gastrointestinal yes ❍ no ❍
Others: ..... if yes, how many: ⌊ ⌋

WHO-Performance Score / ECOG

Grade: ⌊ ⌋

0 = asymptomatic, normal activity
1 = symptomatic, but able to carry out light work
2 = symptomatic, < 50% confined to bed
3 = symptomatic, > 50% confined to bed
4 = completely disabled

Clinic: ..... Signature: .....Date: ⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋.⌊ ⌋⌊ ⌋

Patient initials: ___

MCL elderly/HOVON 55 MCL Efficacy of maintenance therapy after induction (R-CHOP vs. R-FC) for elderly patients with mantle cell lymphoma not suitable for autologous stem cell transplantation **Fax: +31.10.4391028**	**Form 03 / 04** ***registration form***

Clinic-No.: 4 9 4 Patient-No.: ___ Date of birth: __.__.__

INCLUSION CRITERIA / EXCLUSION CRITERIA

Inclusion criteria

Previously untreated patients ..... yes ❍ no ❍

Measurable disease (if only BM infiltration, patients can only undergo a second randomization if a CR is obtained) ..... yes ❍ no ❍

Patients not eligible for autologous stem cell transplantation ..... yes ❍ no ❍

Exclusion criteria

Known autoimmune hemolytic anaemia or autoimmune thrombocytopenia ..... yes ❍ no ❍

Patients with CNS involvement ..... yes ❍ no ❍

Concomitant malignancies other than basal cell skin cancer or in situ cervical cancer ..... yes ❍ no ❍

Serious disorders (uncontrolled infection, serious pulmonary or cardiac disease, psychological impairment etc.) ..... yes ❍ no ❍

Creatinine > 2 x normal value (not due to lymphoma) ..... yes ❍ no ❍

Liver enzymes > 3 x normal or bilirubin > 2,5 x mg/dl (not due to lymphoma) ..... yes ❍ no ❍

Serious depression or neurological disorder ..... yes ❍ no ❍

Chronic hepatitis B or C or HIV infection ..... yes ❍ no ❍

Known antimurine antibody (HAMA) reactivity or known hypersensitivity ..... yes ❍ no ❍

Patient initials: ___

MCL elderly/HOVON 55 MCL

Efficacy of maintenance therapy after induction
(R-CHOP vs. R-FC)
for elderly patients with mantle cell lymphoma
not suitable for autologous stem cell transplantation

Fax: +31.10.4391028

Form 04 / 04

registration form

Clinic-No.: 4 9 4 Patient-No.: ___ Date of birth: __.__.__

BLOOD COUNT

Date: __.__.__

Hb	.....	g/100 ml*
Thrombocytes	.....	/µl
Leucocytes	.....	/µl
Neutr. granulocytes	.....	%
Lymphocytes	.....	%
B-lymphocytes	.....	/µl
T-lymphocytes	.....	/µl

* to translate mmol/l to g/100 ml multiply by 1,61

SERUM

Date: __.__.__

			max. normal value	
Total protein	.....	g/100 ml		
Albumin	.....	g/100 ml		
LDH	.....	U/l	.....	U/l
β_2-microglobulin (optional)	.....	mg/l	.....	mg/l

Clinic: ..... Signature: ..... Date: __.__.__

Appendix F: Molecular Diagnostics Form

European MCL Study Group
Covering Form for Molecular Investigation
Elderly patients > 65 years

Dr. J.J.M. van Dongen
Erasmus University Medical Center Rotterdam
Immunology/Molecular Unit
Dr. Molewaterplein 50
Rotterdam 3015 GE
The Netherlands

Phone:+31-10-4088094

Received:

Patient:

Birth date

Code-No.

Name and Address of hospital/doctor

Tel.: FAX:

Randomisation: [ ] R-CHOP [ ] R-FC

[ ] maintenance Rituximab [ ] maintenance Interferon

Date of sample collection: ...../...../.....

Leucocyte count:...../nl **Blood lymphocytes:**.....%

Material:

[ ] lymph node biopsy (diagnostic specimen)
[ ] clotted sample for serum (only at diagnosis)
[ ] peripheral blood (20 ml in EDTA or citrate for PCR)
[ ] bone marrow aspirate (3-5 ml in EDTA or citrate for PCR)
[ ] peripheral blood (30 ml Heparin for FACS)
[ ] bone marrow aspirate (3-5 ml Heparin for FACS)
[ ] 4 bone marrow slides (air dried and unfixed for FISH)

Time point:

[ ] initial staging; **before** treatment
[ ] staging following halfway induction
[ ] staging following 6 (8) cycles of induction
[ ] maintenance [ ] months after treatment

Date, **Signature**

Appendix G: Serious Adverse Event (SAE) Form

surname: ☐ first name: ☐

TRIAL OF MANTEL CELL LYMPHOMA study: HOVON 55 MCL **REPORT ON A SERIOUS ADVERSE EVENT (SAE)**	**communication:** HOVON Data Center Erasmus MC - Daniel den Hoed P.O. Box 5201 NL-3008 AE ROTTERDAM Fax: +31.10.4391028 Tel: +31.10.4391568

Clinic-No.: ☐☐☐ **Patient-No.:** ☐☐☐ **Date of birth:** ☐☐.☐☐.☐☐. Sex: ○ female ○ male

Contact/Physician:..... **Phone (physician):**.....

report, process and therapy of the serious adverse event:

Begin: ☐☐.☐☐.☐☐ Finish: ☐☐.☐☐.☐☐

(comments:)

Event serious, because:
- ☐ constant physical handicap
- ☐ hospitalization or intensive care by acute reason
- ☐ incidence of conditional anomalies /congenital defect
- ☐ lethal process
- ☐ life threatening
- ☐ secondary malignity

Success of the SAE:
- ☐ restored to health
- ☐ permanent disease
- ☐ recovery
- ☐ unknown
- ☐ degradation
- ☐ decreased

Date of death: ☐☐.☐☐.☐☐ Cause of death:.....