# Clinical Study Report

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| **Clinical Trial:** | PHASE II TRIAL OF RITUXIMAB PLUS 2CdAIN PATIENTS WITH ADVANCED OR RELAPSED LYMPHOMA OF THE MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT) |
| **Clinical Phase:** | II |
| **Protocol Number:** | AGMT_MALT |
| **EudraCT:** | 2008-000767-41 |
| **Coordinating Investigator:** | Univ.-Prof. Dr. Markus Raderer<br>Medizinische Universität Wien<br>Universitätsklinik für Innere Medizin I<br>Klin. Abteilung für Onkologie<br>Währinger Gürtel 18-20, 1090 Wien<br>e-mail: markus.raderer@meduniwien.ac.at |
| **Sponsor:** | AGMT gemeinnützige GmbH<br>Prim. Univ.-Prof. Dr. Richard Greil<br>Universitätsklinik für Innere Medizin III<br>Universitätsklinikum der PMU<br>Salzburger Landeskliniken<br>Müllner Hauptstraße 48, 5020 Salzburg |
| **Sponsor Contact:** | Dr. Daniela Wolkersdorfer<br>Tel.: 0664 1422504<br>e-mail: d.wolkersdorfer@agmt.at |
| **Study initiation date (FPI)** | 09.07.2008 |
| **Study completion date (LPO)** | 28.09.2011 |

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| Dr. Judith Schuster<br>(Projektmanager) | 12-Aug-2013<br>date, signature |
| Dr. Daniela Wolkersdorfer<br>(Clinical Trials Lead Manager AGMT) | 020ct 2013<br>date, signature |
| Prim. Univ.-Prof. Dr. Richard Greil<br>(Head of AGMT) | date, signature |
| Univ.Prof.Dr. Markus Raderer<br>Coordinating Investigator | 12-Aug-13<br>date, signature |

# Content

## 1. Ethics

The study was conducted in accordance with GCP and all applicable local laws and the Declaration of Helsinki, including archiving of study documents.

The study protocol was approved by the lead ethical committees as well as by the local ethical committees of the participating institutions and registered at *www.clinicaltrials.gov (NCT00656812)* before being started. All patients gave written informed consent according to institutional guidelines.

## 2. Rationale for Performing the Study

Currently, there is no chemotherapeutic standard treatment for patients with MALT lymphoma either presenting with disseminated disease or with relapsing/refractory disease following local treatment (including radiation) or eradication of HP. Various compounds have been tested, including alkylating agents such as cyclophosphamide or chlorambucil, the nucleoside analog cladribine (2CdA), as well as combination regimens including CHOP or MCP (mitoxantrone, chlorambucil, prednisone), but only limited data exists from prospective trials. Thus, trials to evaluate the potential of new compounds in patients with advanced MALT lymphoma are not only justified, but seem warranted.

While systemic approaches were until recently thought to be justified only in patients with disseminated disease, emerging data suggest that also patients with localized disease potentially amenable to radiation may benefit from systemic treatment. This has been demonstrated for ocular adnexal MALT lymphoma and recently also for gastric MALT lymphoma in a randomized fashion, where application of chemotherapy resulted in a significantly longer time to relapse as opposed to surgery or radiation without impairing overall survival (25).

Both 2CdA and rituximab have been demonstrated as active single agents in MALT lymphoma with mild toxicity profiles and no data on combination therapy with rituximab plus chemotherapy in MALT lymphoma have been published to date.

## 3. Study objectives

### 3.1 Primary Objective

- To evaluate the feasibility of rituximab plus 2 CdA to induce objective responses in patients with MALT lymphoma.

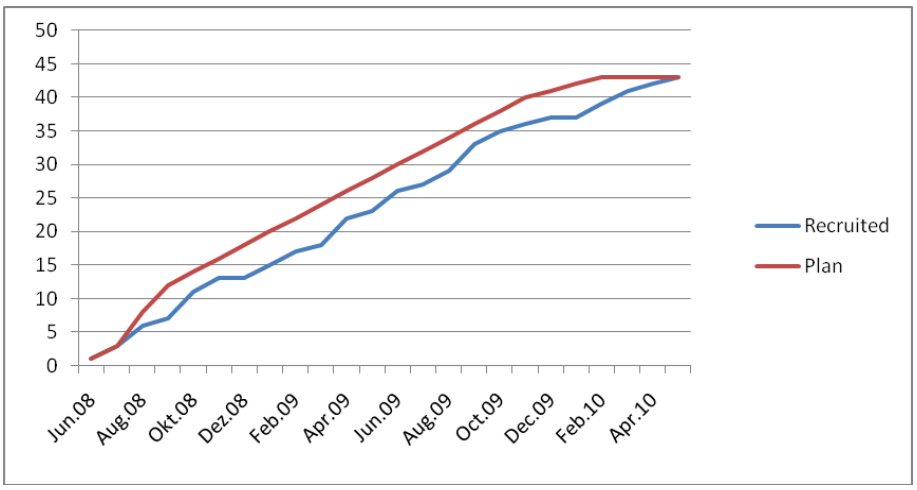
### 3.2 Secondary Objective

- To evaluate the activity of rituximab plus 2CdA on progression-free survival (PFS) and relapse-free survival (RFS).
- To evaluate the safety of the combination therapy.

## 4. Study duration and enrolment

Between July 2008 and September 2011 43 patients have been enrolled.

**Figure 1: Study recruitment**



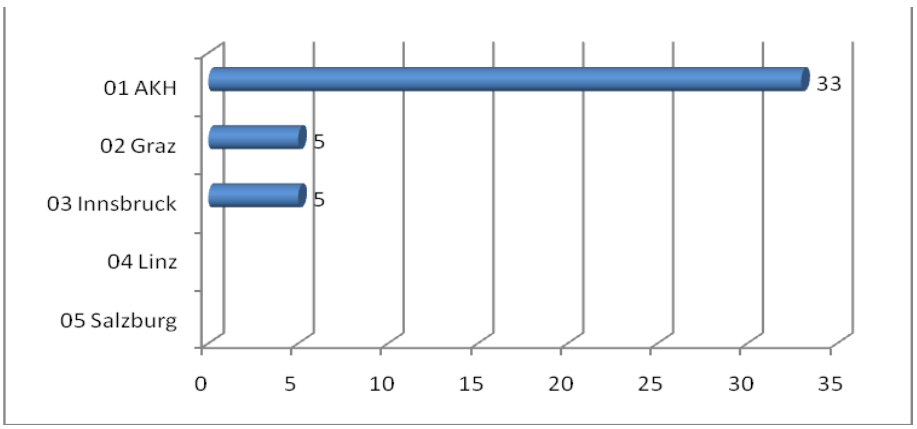

## 5. Investigators and study administrative structure

This is a multicentric study planned to be conducted in 5 study sites.

Study sites are:

1. Universitätsklinik f. Innere Medizin I, AKH Wien – Prof.Dr. Raderer
2. Universitätsklinik f. Innere Medizin, Graz - Prof.Dr. Jäger† followed by Dr. Zebisch
3. Universitätsklinik f. Innere Medizin, Innsbruck – Prof.Dr. Willenbacher
4. Innere Medizin III, AKH Linz, - Prof.Dr. Fridrik
5. Abteilung f. Innere Medizin III, Universitätsklinikum der PMU, Salzburg – Prof.Dr. Greil

**Figure 2: Enrollment of participating sites**



## 6. Study design and methods

Patients with histologically verified MALT lymphoma according to the criteria outlined in the recent WHO-classification of lymphoid malignancies were eligible for the study. In patients with localized gastric MALT lymphoma, documented refractoriness of the lymphoma to HP eradication (i.e. no change after a minimum follow-up of 12 months after successful eradication of the bacteria) was a prerequisite for inclusion in the trial. Patients with extragastric MALT lymphoma or HP-negative gastric MALT lymphoma (in terms of histology and serology) were eligible directly. Patients included in the trial had to be older than 18 years with a WHO performance status ≤2; adequate function of the kidneys (serum creatinine <1.5 mg/dL), liver (total bilirubin <2.0 mg/dL and transaminase level <two times the upper limits of normal) and bone marrow (leukocyte count >3x109/L, platelet count >100x109/L) was also a prerequisite for study entry and application of each cycle of therapy.

Patients with severe concomitant diseases including a history of another malignancy within 5 years before potential inclusion in the study, florid infections, psychiatric disorders or peripheral neuropathies were not eligible. For female patients of childbearing age, a pregnancy had to be excluded before inclusion in the trial, and patients were required to use adequate contraception throughout the whole duration of treatment.

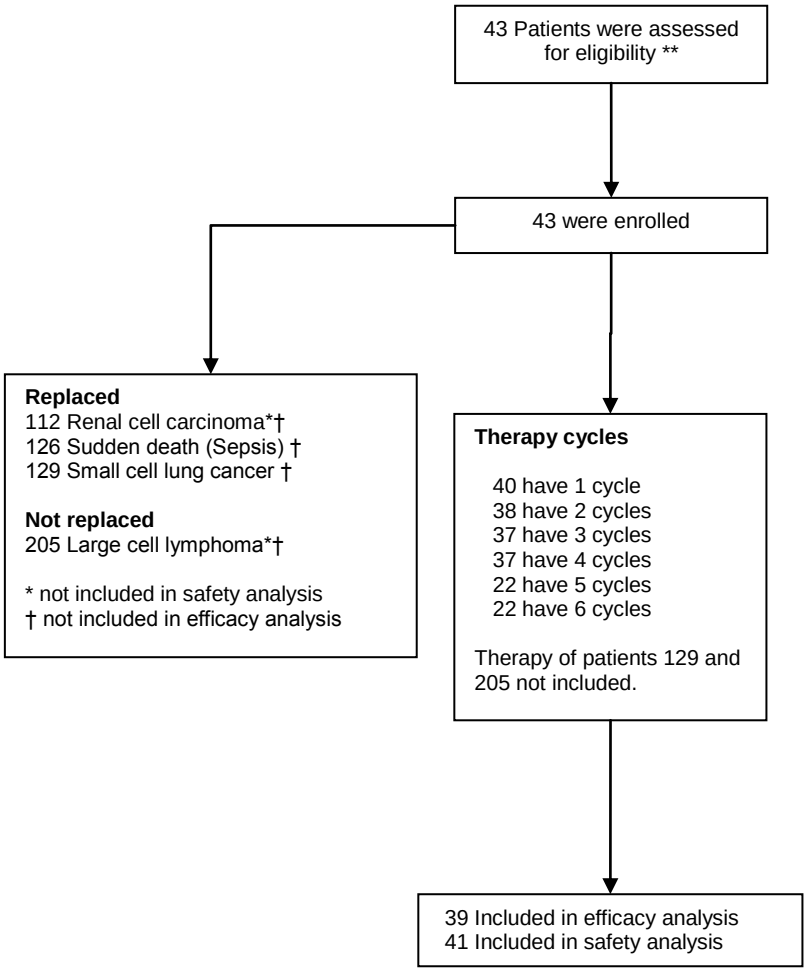
Before administration of therapy, patients underwent staging consisting of imaging of orbital and salivary glands (in patients with non-gastric MALT lymphoma) and computed tomography (CT) scans of the thorax and abdomen, while patients with gastrointestinal lymphoma also underwent gastroscopy (plus endosonography if available) and colonoscopy. Blood counts and renal and hepatic parameters were evaluated immediately before each cycle, while nadir levels of leukocytes with differential, platelets, hemoglobin and erythrocytes were also measured on day 10 – 14 of each cycle.

Treatment consisted of rituximab (Mabthera®, Roche Austria) given at a dose of 375 mg/m2 i.v. on day 1 of each cycle and cladribine (Litak®, Lipomed, Switzerland) at a dose of 0.1 mg/kg administered by s.c. injection on days 1 – 4. Premedication consisted of 1000 mg paracetamol and an antihistaminic drug i.v. before rituximab and a 5-HT3 antagonist (either ondansetron or tropisetron i.v.) immediately before the cladribine. Both rituximab and cladribine were provided free of charge for the trial. Cycles were repeated every 21 days, and restaging was performed after every two cycles of therapy. The primary endpoint of the study was an objective response to therapy. Complete remission (CR), partial response (PR), stable disease and progressive disease were assessed according to RECIST 1.1 criteria; in patients with lymphoma restricted to the stomach, response was assessed by endoscopy with histological sampling according to the histological GELA-criteria10 for CR, stable disease, responding residual disease and probable minimal residual disease. Secondary endpoints were side effects and time to progression. Restaging was performed after two courses of therapy; patients with progressive disease were taken off study, while patients with stable disease, PR or CR were scheduled for another two courses of treatment. In patients with CR after four cycles, treatment was stopped, while patients with PR or SD received another two cycles to a maximum of six cycles.

All patients were followed for at least another 12 months by regular follow-up assessments every 3 months. Depending on the initial diagnosis the follow-up assessments comprised gastroscopy plus CT of the thorax and abdomen for gastric MALT lymphoma, CT or magnetic resonance imaging for extragastric MALT lymphoma and colonoscopy plus CT of the thorax and abdomen for intestinal lymphoma.

## 6.1 Enrolment and outcomes

**Figure 3: Enrolment and outcomes**




** In this study, 40 evaluable patients were required to estimate with sufficient precision the proportion of patients responding to treatment. Patients who were withdrawn within the first 2 months of the study (i.e., before the time point of response evaluation) were replaced.

## 7. Basic characteristics

A total of 43 patients were enrolled in the trial, but three were excluded and replaced according to protocol because, during the initial staging, one was found to have renal cell carcinoma and another was found to have small cell lung cancer, while the third patient was diagnosed with a large cell lymphoma after further path histological assessment of the material.
Baseline characteristics of the 40 evaluable patients are summarized in table 1.

**Table 1: Basic characteristics (Intent-to-treat population n=40)**

| | |
|---|---|
| Age (years) | |
| Median | 61 |
| Range (min-max) | 37 – 78 |
| Interquartile range | 47 - 64 |
| Gender (n) | |
| Female | 14 |
| Male | 26 |
| Stage (n) | |
| I/II | 31 |
| III/IV | 9 |
| Primary site (n) | |
| Gastric | 21 |
| Non-Gastric | 19 |
| Prior systemic treatment (n) | |
| Yes | 10 |
| No | 30 |
| Translocation 11; 18 (n) | |
| Yes | 5 |
| No | 18 |
| Unknown | 16 |
| Bulky disease (n) | |
| Yes | 1 |
| No | 39 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status (n) | |
| ECOG PS 0 | 31 |
| ECOG PS 1 | 9 |

26 patients were male and 14 female, with a median age of 61 years (IQR: 47-64). At study entry, all patients had a good performance status, i.e. ECOG PS 0 or 1. Twenty-one patients (53%) had gastric MALT lymphoma while the remaining 19 cases had no gastric MALT lymphoma including six patients with pulmonary, five with ocular adnexal, four with intestinal and two with salivary gland lymphoma, while one patient each had MALT-lymphoma of the skin and the breast. All patients with gastric MALT lymphoma had been pretreated with HP-eradication, while 10/40 patients (25%) had been pretreated with chemotherapy and 4/40 (10%) patients with radiation therapy. In eight patients, surgery had been performed at initial diagnosis for retrieval of tissue leading to the diagnosis. Only two patients had been pretreated with a rituximab-containing regimen. At the time of study entry, nine patients had disseminated MALT lymphoma, while the remaining presented with localized disease.

## 8. Results

Of the 40 patients judged evaluable, 23 (58%) had a CR, while nine (23%) achieved a PR, resulting in an overall response rate of 81%. Five out of the 40 patients (13%) had stable disease, while three patients were rated as having progressive disease. Of these latter, one patient developed transformation to diffuse large B-cell lymphoma, one patient progressed after one cycle and one patient died before initiation of treatment and was rated as having progressive disease in the intention-to-treat analysis.

Eighteen of the 21 patients (86%) with gastric MALT lymphoma responded to treatment, with 16 patients (76%) achieving a CR and two patients (10%) a PR. The response rate among patients with non-gastric MALT lymphomas was 74% (14/19 patients) with seven CR and 7 PR. The CR were seen after two cycles in 11 patients (9 in gastric and 2 in non-gastric cases); however, some patients subsequently achieved a CR after completion of six cycles of treatment or up to 3 months after the end of treatment Seven of nine patients (78%; CR in 5 patients, PR in 2 patients) with advanced stage lymphoma (stage III and IV) responded to treatment and 25 of 31 patients with localized disease (81%; CR in 18 and PR in 7) showed a response. Eighty percent of systemically pretreated patients had a response (8/10 patients; 4 CR, 4 PR); likewise, 80% of previously untreated patients had a response (24/30 patients; 19 CR, 5 PR).
Treatment-related toxicities were mainly hematologic, with grade III and IV leukopenia in 11/40 (28%) patients, isolated grade III or IV lymphopenia in 4/40 (10%), and grade III anemia and thrombocytopenia in one patient each. Two patients did, however, develop prolonged severe pancytopenia requiring repeated transfusions of packed erythrocytes in both patients and platelet transfusions in one case, as well as repetitive administration of granulocyte colony-stimulating factor. Bone marrow biopsy was not suggestive of myelodysplastic syndrome. The latter patient died 11 months after finishing treatment due to myocardial infarction with ongoing pancytopenia. The other patient recovered fully with normal blood counts 13 months after the last treatment. Grade III fatigue was documented in one patient. Two patients had a grade III allergic reaction during the initial infusion of rituximab and one of these reactions required hospitalization. However, none of these patients had another serious adverse reaction during the following courses of therapy. As a consequence of diarrhea (grade II) one patient developed grade III renal failure, but recovered fully after treatment. Two patients had herpes zoster reactivation and were hospitalized for treatment. One patient developed pneumonia without underlying leukopenia.
One patient showed grade II hypertension resulting in short-term hospitalization. After a median follow-up of 16.7 months (IQR; 15.9 – 18.7 months), one patient has relapsed, with the time to relapse being 8 months. Thus, the median time to progression or time to next treatment has not been reached in our patients. Currently, 35 patients are alive, while four patients have died (one patient from a septic event before administration of therapy, one patient from pneumonia, one due to myocardial infarction, and one because of progression of lymphoma); one patient withdrew consent after completion of therapy and did not allow further follow up.

### 8.1 Detailed toxicity and safety results

Laboratory/vital signs abnormalities were not to be reported as adverse events unless any criterion for a SAE is fulfilled, and laboratory/vital signs abnormality causes the subject to discontinue from the study or the investigator insisted the abnormality should be reported as an adverse event.

Common Terminology Criteria for Adverse Events v3.0 (CTCAE) were used to report and document toxicity and serious adverse events.

## 34 patients experienced adverse events (83%) but no SUSARS occurred during this study.

5,2 % of all adverse events were classified as grade 4 and 18% as grade 3. 8,7% were probably and 8,1% definitely related to study medication MabThera, while 32% were probably and 24,4% definitely related to study medication, respectively.

**Table 2: Listing of SAEs occurred during study treatment**

| SAE | CTC GRADE | Relation | OUTCOME | SUSAR |
|---|---|---|---|---|
| Pneumonia | 3 | no | persisting | no |
| Hypertensive crisis | 2 | no | resolved | no |
| Hypersensitivity (collaps) | 3 | yes | resolved | no |
| Herpes zoster | na | no | na | no |
| Death - multiorgan failure | 4 | no | fatal | no |
| Acute renal failure | 2 | no | resolved | no |
| Herpes zoster | na | yes | persisting | no |
| Small cell lung cancer | 4 | no | persisting | no |
| Hypertensive crisis | | no | resolved | no |

**Table 3: Listing of all AEs occurred during study treatment**

| Adverse Event | Total | unk | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| Allergic reaction/hypersensitivity | 2 | | | | 2 | |
| Aspiration pneumonia | 1 | 1 | | | | |
| Chills | 1 | | 1 | | | |
| CMV-Reaktivation | 2 | | | 2 | | |
| Constipation | 4 | | 4 | | | |
| Cough, productive | 1 | | 1 | | | |
| Death - multiorgan failure | 1 | | | | | 1 |
| Depression | 1 | | 1 | | | |
| Diarrhea | 1 | | | 1 | | |
| Dizziness | 1 | | 1 | | | |
| Dyspnea | 2 | | 1 | 1 | | |
| Exanthema | 2 | | 2 | | | |
| Exsiccosis | 1 | 1 | | | | |
| Fatique | 8 | | 5 | 2 | 1 | |
| Fever | 3 | | 2 | 1 | | |
| Fever (without neutropenia) | 1 | | 1 | | | |
| Hand-foot-skin reaction | 1 | | 1 | | | |
| Hemoglobin | 10 | | 8 | 1 | 1 | |
| Herpes zoster | 3 | 2 | | 1 | | |
| Hypercalcemia | 1 | | | 1 | | |
| Hypertension | 3 | | 1 | 1 | 1 | |
| Hypoglycemia | 1 | 1 | | | | |
| Infection - E.coli sepsis | 1 | | | | | 1 |
| Infection (ANC unk.) - Borreliose | 1 | | | 1 | | |
| Infection (ANC unk.) - pus rooth canla inflammatio | 1 | | | 1 | | |
| Infection (ANC unk.) - Rhinitis | 2 | | 2 | | | |
| Infection (ANC unk.) - Sinusitis | 1 | | | 1 | | |

| Adverse Event | Total | unk | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| Infection, H.pylori + gastritis | 1 | | | 1 | | |
| Insomnia | 3 | | 3 | | | |
| Leukocytes | 43 | | 7 | 20 | 14 | 2 |
| Lymphocytes | 20 | | 5 | 9 | 4 | 2 |
| Lymphopenia | 4 | | | 2 | 2 | |
| Meteorism | 1 | | 1 | | | |
| Mucositis | 1 | | 1 | | | |
| nasal/paranasal reactions - swelling | 1 | | | 1 | | |
| Nausea | 3 | | 2 | 1 | | |
| Neutrophils/granulocytes | 11 | | 4 | 2 | 3 | 2 |
| Pain due to reduction of cortisone | 1 | | 1 | | | |
| Pain gastrointestinal | 2 | | 2 | | | |
| Pain musculoskeletal - Backache | 1 | | | 1 | | |
| Pain pelvis, back | 1 | | 1 | | | |
| Pain tooth | 1 | | 1 | | | |
| Platelets | 13 | | 12 | | 1 | |
| Pneumonia | 1 | | | | 1 | |
| Reinfection Helicobacter pylori | 1 | | 1 | | | |
| Renal failure | 1 | | | | 1 | |
| Skin- exanthema both legs | 1 | | 1 | | | |
| Small cell lung cancer | 1 | | | | | 1 |
| Sweating | 1 | | | 1 | | |
| Tiredness | 1 | | | 1 | | |
| Vomiting | 1 | | 1 | | | |
| **Total** | **172** | **5** | **74** | **53** | **31** | **9** |
| **%** | | **2,9** | **43,0** | **30,8** | **18,0** | **5,2** |

**Table 4: Relation of AEs to study medication MabTherea**
0=unrelated, 1=unlikely, 2=possible, 3=probable, 4=definite

| Adverse event | unk | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Allergic reaction/hypersensitivity | | | | | 1 | 1 |
| Aspiration pneumonia | | 1 | | | | |
| Chills | | | | | | 1 |
| CMV-Reaktivation | | | | | 2 | |
| Constipation | | 4 | | | | |
| Cough, productive | | | 1 | | | |
| Death - multiorgan failure | 1 | | | | | |
| Depression | | 1 | | | | |
| Diarrhea | | 1 | | | | |
| Dizziness | | | 1 | | | |

| Adverse event | unk | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Dyspnea | | 1 | 1 | | | |
| Exanthema | | | | | 1 | 1 |
| Exsiccosis | | 1 | | | | |
| Fatique | | 4 | 2 | 2 | | |
| Fever | | | 1 | 2 | | |
| Fever (without neutropenia) | | | | | | 1 |
| Hand-foot-skin reaction | | | | 1 | | |
| Hemoglobin | | 10 | | | | |
| Herpes zoster | 2 | | | | | 1 |
| Hypercalcemia | 1 | | | | | |
| Hypertension | | 1 | 1 | | | 1 |
| Hypoglycemia | | 1 | | | | |
| Infection - E.coli sepsis | 1 | | | | | |
| Infection (ANC unk.) - Borreliose | | | 1 | | | |
| Infection (ANC unk.) - pus rooth canla inflammatio | | 1 | | | | |
| Infection (ANC unk.) - Rhinitis | | 1 | | 1 | | |
| Infection (ANC unk.) - Sinusitis | | | 1 | | | |
| Infection, H.pylori + gastritis | | 1 | | | | |
| Insomnia | | 3 | | | | |
| Leukocytes | | 26 | 8 | | 9 | |
| Lymphocytes | 1 | 13 | 2 | | 1 | 3 |
| Lymphopenia | | | | | | 4 |
| Meteorism | | 1 | | | | |
| Mucositis | | | | 1 | | |
| nasal/paranasal reactions - swelling | | 1 | | | | |
| Nausea | | 2 | 1 | | | |
| Neutrophils/granulocytes | | 11 | | | | |
| Pain due to reduction of cortisone | | 1 | | | | |
| Pain gastrointestinal | | 2 | | | | |
| Pain musculoskeletal - Backache | | | 1 | | | |
| Pain pelvis, back | | | | | | 1 |
| Pain tooth | | 1 | | | | |
| Platelets | 1 | 11 | 1 | | | |
| Pneumonia | | | 1 | | | |
| Reinfection Helicobacter pylori | | 1 | | | | |
| Renal failure | | 1 | | | | |
| Skin- exanthema both legs | | | | | 1 | |
| Small cell lung cancer | | 1 | | | | |
| Sweating | | | 1 | | | |
| Tiredness | | | | 1 | | |
| Vomiting | | 1 | | | | |
| | | | | | | |

| Adverse event | unk | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| **% of total (n=172)** | **4,1** | **60,5** | **14,0** | **4,7** | **8,7** | **8,1** |

**Table 5: Relation of AEs to study medication Litak**
0=unrelated, 1=unlikely, 2=possible, 3=probable, 4=definite

| Adverse event | Unk | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Allergic reaction/hypersensitivity | | | 2 | | | |
| Aspiration pneumonia | | 1 | | | | |
| Chills | | 1 | | | | |
| CMV-Reaktivation | | | | | | 2 |
| Constipation | | 2 | 2 | | | |
| Cough, productive | | | 1 | | | |
| Death - multiorgan failure | 1 | | | | | |
| Depression | | 1 | | | | |
| Diarrhea | | | | | 1 | |
| Dizziness | | | 1 | | | |
| Dyspnea | | 1 | 1 | | | |
| Exanthema | | 1 | 1 | | | |
| Exsiccosis | | 1 | | | | |
| Fatique | | 4 | 1 | 3 | | |
| Fever | | | 1 | 2 | | |
| Fever (without neutropenia) | | 1 | | | | |
| Hand-foot-skin reaction | | | 1 | | | |
| Hemoglobin | | 3 | | | 5 | 2 |
| Herpes zoster | 2 | | | | | 1 |
| Hypercalcemia | 1 | | | | | |
| Hypertension | | 2 | 1 | | | |
| Hypoglycemia | | 1 | | | | |
| Infection - E.coli sepsis | 1 | | | | | |
| Infection (ANC unk.) - Borreliose | | | 1 | | | |
| Infection (ANC unk.) - pus rooth canla inflammatio | | 1 | | | | |
| Infection (ANC unk.) - Rhinitis | | 1 | | 1 | | |
| Infection (ANC unk.) - Sinusitis | | | 1 | | | |
| Infection, H.pylori + gastritis | | 1 | | | | |
| Insomnia | | 3 | | | | |
| Leukocytes | | | 6 | 1 | 20 | 16 |
| Lymphocytes | 1 | | | | 11 | 8 |
| Lymphopenia | | | | | | 4 |
| Meteorism | | 1 | | | | |
| Mucositis | | | | | 1 | |
| nasal/paranasal reactions - swelling | | 1 | | | | |

| Adverse event | Unk | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Nausea | | 1 | | | 2 | |
| Neutrophils/granulocytes | | | | | 3 | 8 |
| Pain due to reduction of cortisone | | 1 | | | | |
| Pain gastrointestinal | | 1 | | | 1 | |
| Pain musculoskeletal - Backache | | | 1 | | | |
| Pain pelvis, back | | 1 | | | | |
| Pain tooth | | 1 | | | | |
| Platelets | 1 | 1 | | | 10 | 1 |
| Pneumonia | | | 1 | | | |
| Reinfection Helicobacter pylori | | 1 | | | | |
| Renal failure | | | 1 | | | |
| Skin- exanthema both legs | | 1 | | | | |
| Small cell lung cancer | | 1 | | | | |
| Sweating | | | 1 | | | |
| Tiredness | | | | 1 | | |
| Vomiting | | | | | 1 | |
| | | | | | | |
| **% of total (n=172)** | **4,1** | **20,9** | **14,0** | **4,7** | **32,0** | **24,4** |

### 8.2 Response Assessment

- Complete remission (CR): Complete disappearance of all previously detectable manifestations of disease and no evidence for new lesions.
- Partial remission (PR): Reduction of at least 50 % of lymphoma manifestations (sums of the products of the biperpendicular diameters of all measurable disease). In addition, no increase in size of any other lesion (measurable or non-measurable) nor the appearance of new lesions must be observed.
- Stable disease (SD): Less than 50 % reduction and less than 25% increase in the sums of the products of the biperpendicular diameters of all measurable disease and no new lesions.
- Progressive disease (PD): An increase in size of more than 25% of previously documented disease, or the appearance of new lesions.

Continuation of treatment after cycle 2 and 4 was only allowed after completed response evaluation.

**Table 6: Response rate**

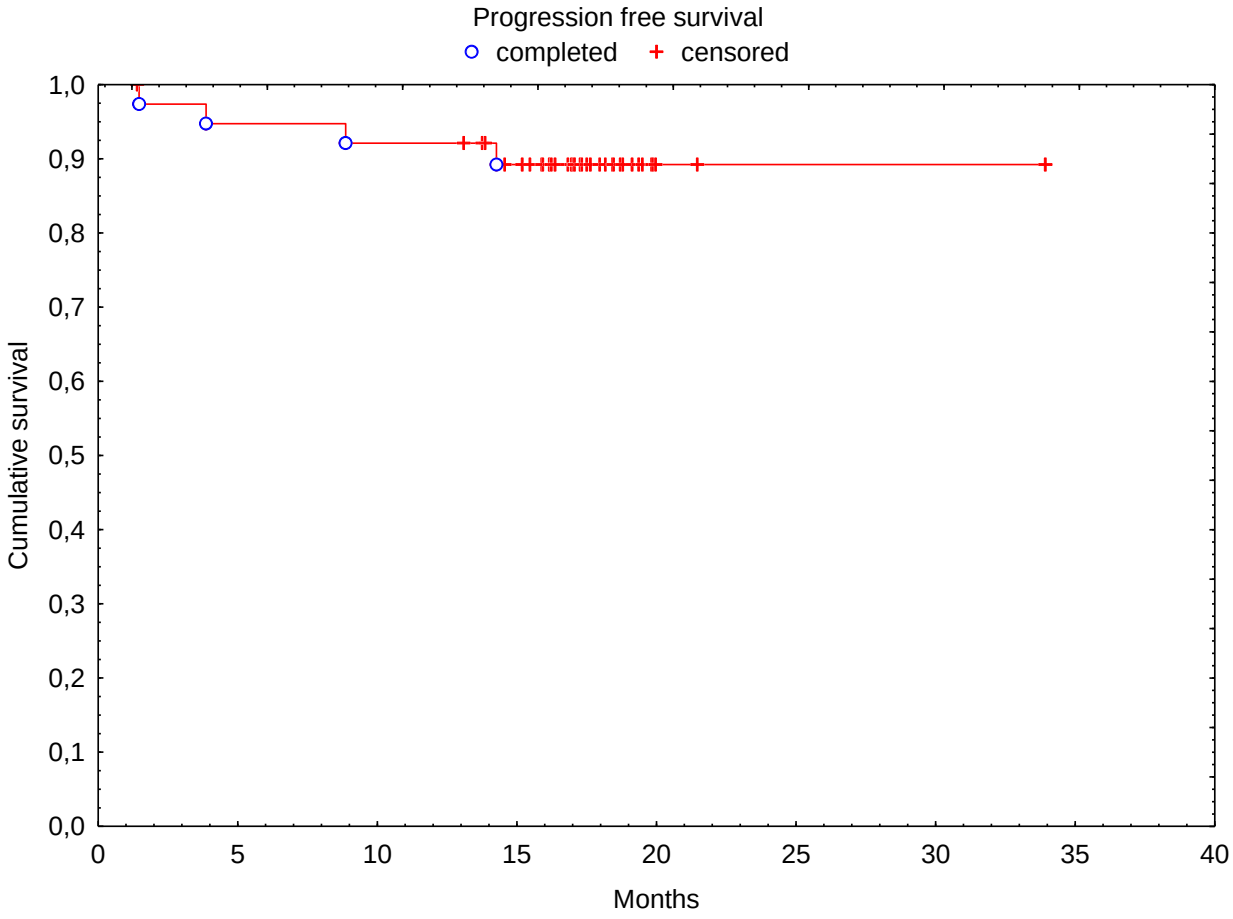
| Response rate | N. of patients (%) |
|---|---|
| Overall | 32 (81) |
| Partial remission | 9 (23) |
| Complete remission | 23 (58) |
| Gastric MALT Lymphoma | 21 |
| Overall | 18 (86) |
| Partial remission | 2 (10) |
| Complete remission | 16 (76) |
| Non gastric | 19 |
| Overall | 14 (74) |
| Partial remission | 7 (37) |
| Complete remission | 7 /37) |
| Advanced stage | 9 |
| Overall | 7 (78) |
| Partial remission | 2 (22) |
| Complete remission | 5 (56) |
| Localized stage | 31 |
| Overall | 25 (81) |
| Partial remission | 7 (23) |
| Complete remission | 18 (58) |
| Pretreated patients | 10 |
| Overall | 8 (80) |
| Partial remission | 4 (40) |
| Complete remission | 4 (40) |
| Untreated patients | 30 |
| Overall | 24 (80) |
| Partial remission | 5 (17) |
| Complete remission | 19 (63) |

## 8.3 Survival

**Progression-free survival**

The progression-free survival time for each patient is the number of days from the day of first treatment to the earlier: (1) death (from any cause) or progression or (2) the last on-study tumour assessment (including 1-year follow-up period). If the progression-free survival time does not correspond to the patient's death or progression then it is treated as censored.

**Figure 4: Progression free survival (median not reached)**



**Overall survival**

The overall survival time for each patient is the number of days from the day of first treatment to the earlier: (1) death (from any cause) or (2) the last on-study tumour assessment (including 1-year follow-up period). If the overall survival time does not correspond to the patient's death then it is treated as censored.

**Figure 5: Overall survival (median not reached)**