CRAD 001C2428

Phase II study of the mTOR-Inhibitor EVEROLIMUS as maintenance therapy in patients aged over 60 years with Mantle Cell Lymphoma (MCL) after first, second, third or fourth line chemotherapy

Author(s): Prof. Dr. Ulrich Keller, Dr. Susanne Schreiber

Document type: Clinical Study Report

Development phase : II

Investigator(s) : Prof. Dr. Ulrich Keller

First patient recruited : 09/19/2008 Last patient completed: 02/22/2011

Release date: Version 1.0 10/02/2013

Study personell

Sponsor
Technische Universität München (TUM)
Fakultät für Medizin
Ismaninger Straße 22
81675 München

Coordinating Investigator (Leiter Klinische Prüfung, LKP)
Prof. Dr. Ulrich Keller
Klinikum rechts der Isar (MRI) der TUM
III. Medizinische Klinik und Poliklinik Hämatologie / Onkologie
Ismaninger Str. 22
81675 München

Project Management
Münchner Studienzentrum (MSZ)
Ismaninger Straße 22, 81675 München
Phone.089-4140-6321, Fax: 089-4140-6322

Data Management
Münchner Studienzentrum
Ismaninger Straße 22, 81675 München
Tel: 089-4140-6321, Fax: 089-4140-6480

Monitoring
Münchner Studienzentrum
Ismaninger Straße 22, 81675 München
Tel. 089-4140-6321, Fax: 089-4140-6322

Statistics
Dr. Alexander Hapfelmeier
Institut für Medizinische Statistik und Epidemiologie
Ismaninger Straße 22, 81675 München
Tel: 089-4140-4355, Fax: 089-4140-4850
E-Mail: Alexander.hapfelmeier@tum.de

Investigators and centers

1. Klinikum rechts der Isar (MRI) der TUM
III. Medizinische Klinik und Poliklinik Hämatologie / Onkologie
Coordinating Investigator (Leiter Klinische Prüfung, LKP)/Principal Investigator:
Prof. Dr. Ulrich Keller
Ismaninger Str. 22
81675 München
Tel : 089-4140-7435, Fax : 089-4140-6479
E-Mail: ulrich.keller@lrz.tum.de

2. Charité Universitätsmedizin Berlin, Campus Virchow Klinikum
Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie
Principal Investigator: Prof. Dr. Christian Scholz
Augustenburger Platz 1
13353 Berlin
Tel.: 030 450 553 862
030 450 653 862
Fax: 030 450 553 66
E-Mail: christian.scholz@charite.de

3. Robert-Bosch-Krankenhaus Stuttgart (no participation)
Hämatologie / Onkologie
Principal Investigator: Prof. Dr. Walter-Erich Aulitzky
Auerbachstr. 110
70376 Stuttgart
Tel: 0711-8101-3506
Fax: 0711-8101-3796
E-Mail: walter.aulitzky@rbk.de

4. Universitätsklinikum Ulm (no participation)
Hämatologie / Onkologie
Principal Investigator: Prof. Stephan Stilgenbauer

Klinik für Innere Medizin III
Albert-Einstein-Allee 23
89081 Ulm
Tel.: 0731 500 457 13
Fax: 0731 500 244 05
E-Mail: stephan.stilgenbauer@uniklinik-ulm.de

6. Klinikum Großhadern
Hämatologie / Onkologie
Principal Investigator: Prof. Martin Dreyling
Medizinische Klinik III
Marchioninistraße 15
81377 München
Tel.: 089 7095 2202
Fax: 089 7095 2550

E-Mail: martin.dreyling@med.uni-muenchen.de

7. Onkologie Ravensburg
Principal Investigator: PD Dr. Thomas Decker
Elisabethenstraße 19
88212 Ravensburg
Tel.: 0751 366 197 0
Fax: 0751 366 197 66
E-Mail: t.decker@lrz.tum.de

8. Klinikum Traunstein
Principal Investigator: Dr. Thomas Kubin
Cuno-Niggl-Straße 3
83278Traunstein
Tel: 0861 705 1243
Fax:0861 795 1729
E-Mail: Thomas.kubin@klinikum-traunstein.de

9. Praxis Frau Dr. med. Ursula Kronawitter, Dr. med Christoph Jung
Principal Investigator:Dr. med. Ursula Kronawitter
Wasserburger Straße 29
83278 Traunstein
Tel:0861 70879 30
Fax:0861 79879 31
E-Mail: Onkologie-traunstein@t-online.de

Table of contents

List of Tables

List of abbreviations and definition of terms

AE	Adverse Event
Akt	Protein Kinase B
AMG	Arzneimittelgesetz
ANC	Absolute Neutrophile Count
B-NHL	B cell Non-Hodgkin Lymphoma
CD	Cluster of Differentiation
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CR	Complete Remission
CRF	Case Report Form
CRu	Undocumented Complete Remission
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	Cytochrome P450 3A isoenzyme
DNA	Deoxyribonucleic Acid
EAP	Efficacy Analyzable Population
EC	Ethics Committee
ECG	Electrocardiogram
eIF-4E	Eucaryotic Initiation Factor 4E
eIF-4E-BP1	eIF-4E-binding Protein 1
EOS	End of Study
EU	European Union
FC	Fludarabine, Cyclophosphamide
FCM	Fludarabine, Cyclophophamide, Mitoxantrone
FKBP-12	FK506-binding Protein 12
FL	Follicular Lymphoma
G-CSF	Granulocyte Colony-stimulating Factor
GI	gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-stimulating Factor
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
Hyper-CVAD	hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFN-α	Interferon-α
ISMB	Independent Safety Monitoring Board
ITT	Intention to Treat Population
LKP	Leiter klinische Prüfung
mAb	Monoclonal Antibody
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Klinikum rechts der Isar München
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSZ	Münchener Studienzentrum
mTOR	Mammalian Target of Rapamycin

NCI	National Cancer Institute
NIH	National Institute of Health
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PR	Partial Remission
QOL	Quality of Life
QOLq	Quality of Life Questionnaire
R	Rituximab
RCC	Renal Cell Carcinoma
RNA	Ribonucleic Acid
S6K1	S6 Kinase 1
SAE	Serious Adverse Event
SAP	Safety Analyzable Population
SAR	Serious Adverse Reaction
SCT	Stem Cell Transplantation
SD	Stable Disease
SMPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time to Progression
TUM	Technische Universität München
ULN	Upper Limit of Normal

Study Report Synopsis

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin Prof. Dr. med. Peter Henningsen, Dekan
Name of Finished Product: Afinitor®
Name of Active Ingredient: EVEROLIMUS (RAD001)
Title of Study: Phase II study of the mTOR-Inhibitor EVEROLIMUS as maintenance therapy in patients aged over 60 years with Mantle Cell Lymphoma (MCL) after first, second, third or fourth line chemotherapy
Protocol Code: cRad001c2428
EudraCT: 2007-005116-12
Coordinating Investigator: LKP (AMG): Prof. Dr. med. Ulrich Keller
Participating Study Centres: **1.** Klinikum rechts der Isar (MRI) der TUM III. Medizinische Klinik und Poliklinik Hämatologie / Onkologie Coordinating Investigator (Leiter Klinische Prüfung, LKP) / Principal Investigator: Prof. Dr. Ulrich Keller Ismaninger Str. 22 81675 München Tel : 089-4140-4104, Fax : 089-4140-6479 E-Mail: ulrich.keller@lrz.tum.de **2.** Charité Universitätsmedizin Berlin, Campus Virchow Klinikum Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie Principal Investigator: Prof. Dr. Christian Scholz Augustenburger Platz 1 13353 Berlin Tel.: 030 450 553 862 030 450 653 862 Fax: 030 450 553 66 E-Mail: christian.scholz@charite.de **3.** Robert-Bosch-Krankenhaus Stuttgart (no participation) Hämatologie / Onkologie Principal Investigator: Prof. Dr. Walter-Erich Aulitzky Auerbachstr. 110 70376 Stuttgart Tel: 0711-8101-3506 Fax: 0711-8101-3796 E-Mail: walter.aulitzky@rbk.de

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin Prof. Dr. med. Peter Henningsen, Dekan
Name of Finished Product: Afinitor®
Name of Active Ingredient: EVEROLIMUS (RAD001)
4. Universitätsklinikum Ulm (no participation) Hämatologie / Onkologie Principal Investigator: Prof. Stephan Stilgenbauer Klinik für Innere Medizin III Albert-Einstein-Allee 23 89081 Ulm Tel.: 0731 500 457 13 Fax: 0731 500 244 05 E-Mail: stephan.stilgenbauer@uniklinik-ulm.de **6.** Klinikum Großhadern Hämatologie / Onkologie Principal Investigator: Prof. Martin Dreyling Medizinische Klinik III Marchioninistraße 15 81377 München Tel.: 089 7095 2202 Fax: 089 7095 2550 E-Mail: martin.dreyling@med.uni-muenchen.de 7.Onkologie Ravensburg Principal Investigator: PD Dr. Thomas Decker Elisabethenstraße 19 88212 Ravensburg Tel.: 0751 366 197 0 Fax: 0751 366 197 66 E-Mail: t.decker@lrz.tum.de 8. Klinikum Traunstein Principal Investigator: Dr. Thomas Kubin Cuno-Niggl-Straße 3 83278Traunstein Tel: 0861 705 1243 Fax:0861 795 1729 E-Mail: Thomas.kubin@klinikum-traunstein.de 9.Praxis Frau Dr. med. Ursula Kronawitter, Dr. med Christoph Jung Principal Investigator:Dr. med. Ursula Kronawitter Wasserburger Straße 29 83278 Traunstein Tel:0861 70879 30 Fax:0861 79879 31 E-Mail: Onkologie-traunstein@t-online.de

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin Prof. Dr. med. Peter Henningsen, Dekan	
Name of Finished Product: Afinitor®	
Name of Active Ingredient: EVEROLIMUS (RAD001)	
Publication (reference): not published yet	
Studied period (years) **first patient in:** 2008 **last patient out:** 2011 The clinical study was terminated prematurely in 2012 due to slower than anticipated recruitment. On 03/20/2008 protocol version 2.0 (changes from Version 1.0. to 2.0 due to EC request) was approved by the EC. All eight patients included into the clinical trial were included under this protocol version. V.3.0 (allowing enrollment not only of first and second line patients, but also of third and fourth line patients) dating from 09/01/2010 was approved by the EC on 10/25/2010. Current V.4.0 (new data, patient number reduced, reviewed endpoints, descriptive statistics, reviewed table of events) dating from 08/01/2011 was approved by the EC on 09/07/2011. Analysis of the patient population will be performed following the current protocol version 4.0., since this version consists in an amelioration and precision of the older versions.	Non-randomized, open-label, multicentre, Phase II trial

Objectives:

To investigate the efficacy (time to progression) and safety of a maintenance therapy with EVEROLIMUS in patients with MCL aged over 60 years or aged over 40 years but not eligible for high-dose chemotherapy followed by autologous stem cell support or allogeneic stem cell transplantation.

Primary endpoint:

Time to progression despite maintenance therapy with EVEROLIMUS. Start of measurement was defined as last day of application of remission-inducing chemotherapy.

Secondary endpoints:

- To analyze toxicity and feasibility of a treatment with EVEROLIMUS in patients with MCL after first, second, third and fourth line chemotherapy
- To analyze surrogate parameters involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement (only in patients with circulating MCL cells or with bone marrow involvement)
- To compare the duration of previous responses with the duration of responses in

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

patients with maintenance therapy

- To analyze the conversion rate in MCL patients during maintenance therapy (improvement of partial to complete response, stable disease to partial or complete response)
- To analyze the overall survival of patients with maintenance therapy
- To analyze Quality of life during maintenance therapy

Methodology: non-randomized, open-label, multicentre, Phase II trial

Number of patients (planned and analyzed):

Planned sample size: 25 patients

Analyzed sample size: 8 patients (all patients who were included into the trial)

Diagnosis and main criteria for inclusion:

Indication: Mantle Cell Lymphoma (MCL)

Inclusion criteria:

1. Patients with a proven history of mantle cell lymphoma
2. Patients with achieved disease control after one to four lines of chemotherapy (complete response, partial response, stable disease) for mantle cell lymphoma.
3. Patients must have been treated with a CHOP-like chemotherapy or a Fludarabine-containing regimen previously and Rituximab must have been used as part of the previous treatment.
4. Age ≥ 60 years or patients ≥40 and <60 years of age who are not eligible for high-dose chemotherapy followed by autologous stem cell support or allogeneic stem cell transplantation.
5. Minimum of two weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy).
6. WHO performance status ≤ 2
7. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hgb> 9 g/dL
8. Adequate liver function as shown by: serum bilirubin ≤ 1.5 x upper limit of normal (ULN), and serum transaminases activity ≤ 3 x ULN. With the exception of serum transaminases (< 5 x ULN) if the patient has liver metastases
9. Life expectancy of at least 3 months
10. Signed informed consent

Main criteria for exclusion:

Exclusion criteria:

1. Prior treatment with any investigational drug within the preceding 4 weeks
2. Chronic treatment with systemic steroids or another immunosuppressive agent except for Rituximab.
3. Uncontrolled brain or leptomeningeal disease manifestation, including patients

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

who continue to require glucocorticoids for brain or leptomeningeal disease manifestation
4. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
5. Other concurrent severe and/or uncontrolled medical disease which could compromise participation in the study (i.e., uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, unstable angina, or congestive heart failure - New York Heart Association Class III or IV, ventricular arrhythmias active ischemic heart disease, myocardial infarction within six months, chronic liver or renal disease, active upper GI tract ulceration, psychiatric disease)
6. A known history of HIV seropositivity
7. History or serology indicating active or chronic Hepatitis B or C or detection of viral DNA/RNA (Hepatitis. B or C) via PCR
8. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of EVEROLIMUS (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
9. Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumarin)
10. Previous organ transplantation.
11. Women who are pregnant or breast feeding, or women able to conceive and unwilling to practice an effective method of birth control. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of EVEROLIMUS). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. A highly effective methode of birth control is defined as those which results in a low failure rate (i.e. less than 1% per year) for example sexual abstinence or vasectomized partner.
12. Patients who have received prior treatment with an mTor inhibitor.
13. History of noncompliance to medical regimens
14. Patients unwilling to or unable to comply with the protocol
15. Patients with galactose intolerance, lack of lactase or malabsorption of glucose or galactose

Test product, dose and mode of administration, batch number:
EVEROLIMUS in MCL patients, administered orally as single daily dose of 5 mg (5 mg and 2.5 mg tablets).
Batch numbers 975, 9866, 9880 and 10018 (distributed by the pharmacy of Klinikum rechts der Isar)

Duration of treatment / treatment schedule:

Maintenance with EVEROLIMUS (5 mg/d) should be administered continuously for a maximum of 24 months or until disease progression.

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

Study medication had to be interrupted in 2/8 patients. Premature discontinuation of EVEROLIMUS maintenance was necessary due to progression of disease in 2/8 patients, adverse events (AE) or on patients' request in 6/8 patients.

Reference therapy, dose and mode of administration, batch number:

Not applicable (n. a.)

1. Reference substance: n. a.
2. Reference substance: n. a.

Unblinding:
n. a.

Criteria for evaluation:

Primary efficacy parameters

Efficacy was measured by **time to progression** despite maintenance therapy with EVEROLIMUS. The last day of the remission inducing chemotherapy was set to be the first day of measurement. Efficacy was measured by the listed diagnostic measures (CT scan or chest X-ray and abdominal sonography; if clinically indicated, esophagogastroduodenoscopy could be performed).

Secondary efficacy parameters:

- **toxicity and feasibility** of the treatment with EVEROLIMUS in patients with MCL after first, second, third and fourth line chemotherapy
- **surrogate parameters** involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement (only in patients with circulating MCL cells or with bone marrow involvement)
- **comparison of duration of previous responses with duration of responses in patients under maintenance therapy**
- **conversion rate in MCL patients during maintenance therapy (**improvement of partial to complete response, stable disease to partial or complete response)
- **overall survival** of patients with maintenance therapy
- **quality of life** during maintenance therapy

Criteria for assessing efficacy

A modification of the recommendations of an International workshop to standardize response criteria for Non-Hodgkin's lymphoma was applied [Cheson, 1999]. Response criteria were determined as follows:

Complete remission (CR):

CR was defined as complete disappearance of all objective signs of disease including

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

enlarged lymph nodes, as well as hepatomegaly and splenomegaly. In case of improvement of response during the study period, CR had to be documented for at least a period of two months. In case of bone marrow involvement, clearance of bone marrow by lymphoma had to be documented by bone marrow biopsy and normalization of blood counts.

Undocumented complete remission (CRu):

CRu was defined as the disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities and normalization of the performance status. In case of demonstration of persisting lymphoma cells in any puncture or biopsy, the response was defined as partial remission (PR). Similar to CR, CRu had to be documented for a period of at least two months after the end of therapy.

Partial remission (PR):

PR was defined as at least 50% reduction (≥50%) of all measurable and evaluable areas of lymphoma (sum of products of the largest diameters vertical to each other) for at least four weeks without occurrence of new manifestations and normalization of blood counts.

Stable disease (SD)
Tumor regression <50%, no new manifestations and progression ≤25%.

Progressive disease (PD):
Progressive disease was defined as:
- increase of frequency and severity of symptoms
- new nodal manifestations of lymphoma
- enlargement of manifestations of lymphoma more than 25%.

Time to progression (TTP):

Interval between the last day of application of remission-inducing chemotherapy to detection of progressive disease (PD). Furthermore, the time period from start of maintenance therapy with EVEROLIMUS and detection of progressive disease had to be documented.

Safety assessments

Safety assessments consisted of monitoring and recording all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs and the performance of physical examinations. These parameters should have been performed within ±3 days of the study visits except for adverse events that were evaluated continuously throughout the study. Safety and tolerability were assessed according to the NIH/NCI- CTCAEv3.

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

Patients were monitored in the outpatient department on week 1, 2 and 4 during the first month, on months 2, 3 and 6 and every 3 months thereafter. Patients were examined for signs of progressive disease.

Independent Safety Monitoring Board (ISMB)

A group of independent experts formed an Independent Safety Monitoring Board (ISMB).

The ISMB independently reviewed the safety data during study duration. The board was to review the safety data at least once a year and in addition an interim analysis after inclusion of 10 patients was planned to report adverse events and assess the safety profile.

Statistical methods

Data was summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements.

The primary efficacy endpoint was intended to be analyzed using 95% confidence intervals for mean time to progression. The primary analysis was planned to be done separately for patients after first and second line chemotherapy and for patients after third and fourth line chemotherapy.

The assessment of safety was based mainly on the frequency of adverse events (AEs) and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e. g. electrocardiogram, vital signs, special tests) were considered as appropriate.

AEs were planned to be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each body system and having each individual AE.

Any other information collected (e. g. severity or relationship to study medication) will be listed as appropriate.

Due to the observational nature of the study and the total sample size of only N=8 patients, descriptive analyses of efficacy observations and measurements, safety observations and measurements were employed on a case base for all eight patients.

Summary – Conclusions:

Patient Demographics and Patient Disposition

In total, eight patients with a proven history of MCL were included into the study (first patient included: 09/19/2008; last patient included: 10/19/2009. Patients were 63 -80 years of age (median 73 years) and the male/female ratio was 7:1, which confirms a clear predominance of males vs. females suffering from MCL.

With one exception patients had received one or two chemotherapy lines before inclusion into the study, basically CHOP, bendamustin or fludarabin-containing

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

regimens, for MCL treatment before. All patients had been exposed to Rituximab.

None of the eight patients who received study medication are still under maintenance therapy with EVEROLIMUS and none of them completed the designated maintenance period of 24 months. The longest duration of study therapy was 459 days (07/00002). Two patients had to stop EVEROLIMUS maintenance due to disease progression under study medication (documented disease progression 5.2 months [07/00001] and 5.6 months [06/00001] after start of medication). One patient had to be taken off study medication due to medication interaction with the anticonvulsant valproic acid after having suffered an epileptic seizure (01/00001: 0.6 months after start of medication). The other five patients, (01/00002, 06/00002, 07/00002, 07/00003 and 07/00004), prematurely stopped study medication on personal request 0.83 - 15.3 months after start of maintenance therapy. For two patients other reasons for discontinuation of study drug were additionally documented in the CRF. One patient (07/00001) having been taken off study drug due to disease progression developed diplopia as first symptom of progressive disease. Thus for this patient diplopia was indicated as additional reason for discontinuation of EVEROLIMUS besides disease progression. One patient (06/00002) stopped study medication at his own discretion after having developed extrasystoles and atrial fibrillation. He finally discontinued EVEROLIMUS maintenance on personal request due to the suffered atrial fibrillation, specified as “other reason”.

One patient (07/00001) died 9.7 months after inclusion into the study due to disease progression.

Safety (SAP), Intention to Treat (ITT) and Efficacy Analyzable Population (EAP)

Since all patients received at least one dose of EVEROLIMUS all patients were included into the SAP and ITT Population.

For the EAP four patients who received EVEROLIMUS for at least four weeks and who did not violate inclusion or exclusion criteria (07/00001, 07/00002, 07/00003, 07/00004) were included. Patients who received EVEROLIMUS for less than four weeks (01/00001, 01/00002) or violated inclusion criteria (06/00001, 06/00002) were excluded from EAP.

Efficacy Results:
Efficacy had to be measured by CT scan or chest X-ray and abdominal sonography. If clinically indicated esophagogastroduodenoscoy could be performed as well.

Due to the small number of patients included into the study (8 patients), it was decided to present efficacy results of all patients treated in the study in a descriptive manner regardless of their classification in the different analysis populations.

Response to Treatment

Primary outcome: – Time to progression (TTP):

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

5/8 Patients developed documented disease progression during the predefined observation period of two years. Time to progression, as defined in the study protocol (interval between last day of application of remission-inducing chemotherapy to detection of progressive disease), in these patients ranged from 4.7 months (142 days) to 25.6 months (767 days). The period from start of maintenance therapy with EVEROLIMUS and detection of progressive disease ranged from 2.3 months (70 days) to 24.8 months (744 days). The median TTP in our study cohort was 10.1 months (303 days) with a median period from start of maintenance therapy with EVEROLIMUS to detection of progressive disease of 5.6 months (168 days).

Two of the remaining three patients (01/00002 and 07/00003) did not develop disease progression until the end of the protocol-defined observation period of two years after study enrollment (01/00002 documented SD; 07/00003 documented PR).

The remaining third patient (07/00004) was lost to follow-up before having completed the observation period of two years. Until the last documented contact with the respective patient 566 days (18.9 months) after the last day of remission-inducing chemotherapy or 524 days (17.5 months) after start of maintenance therapy with EVEROLIMUS no PD was documented.

Secondary outcomes:

Overall survival:

For overall survival the status of the eight patients 24 months after inclusion was to be considered. 1/8 patients died within two years after enrollment into the study. Patient 07/00001 died 290 days (9.7 months) after study inclusion and 129 days (4.3 months) after maintenance therapy with EVEROLIMUS had been stopped due to documented disease progression. Documented reason for death of the patient was disease progression.
One patient (07/00004) was lost to follow-up 615 days (20.5 months) after study inclusion. Thus, we do not have any information on her survival beyond this date. Two other patients were lost to follow-up after progressive disease (06/00001:182 days after study inclusion; 06/00002; 84 days after study inclusion).
The remaining four patients 01/00001, 01/00002, 07/00002 and 01/00003 were still alive 24 months after study inclusion
As no further follow-up beyond 24 months after study inclusion was foreseen in the study protocol, we do not have any information concerning patients' survival beyond two years after enrollment into the study.

Surrogate parameters:

Since surrogate parameters involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement could have been collected only in patients with these characteristics this analysis was not applicable,

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

since none of these patients were included into the study

Quality of life:

For evaluation of potential changes in quality of life (QOL) during maintenance therapy with EVEROLIMUS patients had to fill in a questionnaire (QOLq) concerning their general health status, including a subjective estimation of their quality of life (QOL), at predefined time points during the study.

7/8 patients filled in QOLqs during participation in the study and the results were assessed on a case by case base. One patient estimated his general health status and QOL slightly improved under maintenance therapy with EVEROLIMUS. One patient noted no significant changes and the other five patients evaluated their general health status and QOL as deteriorated during participation in the study.

Conversion during maintenance with EVEROLIMUS:

Conversion was defined as improvement of partial to complete response or improvement of stable disease to partial or complete response during maintenance therapy with EVEROLIMUS.

1/8 patients showed a conversion under maintenance therapy as defined in the study protocol (PR → CR). Disease status of five patients remained stable and two patients developed disease progression during maintenance with EVEROLIMUS.

Response duration during maintenance therapy in comparison to duration of previous responses:

This comparison could only be done in patients who already underwent two lines of chemotherapy before maintenance with EVEROLIMUS. As the exact date of documented progress was not directly evaluated in the CRF, we present as “previous response” the interval from the end of first or second line therapy to the start of the next treatment line.

In our patient cohort this comparison could be done for three patients. For all tree patients response durations under maintenance therapy with EVEROLIMUS were considerably shorter than response durations after first line chemotherapy.

Safety Results:

Safety information collected included -in addition to adverse events (AE), serious adverse events (SAE) and serious adverse reactions (SAR)- data on performance status, the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs and the performance of physical examinations.

Details on the data that had to be collected are provided in the clinical study protocol (Clinical study protocol: 4.5 Safety assessments).

AEs were graded according to the NIH/NCI CTCAEv3.pdf .

Independent Safety Monitoring Board

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Afinitor®

Name of Active Ingredient: EVEROLIMUS (RAD001)

A group of independent experts formed an Independent Safety Monitoring Board (ISMB).

The ISMB independently reviewed the safety data during study duration. The board was to review the safety data at least once a year and in addition an interim analysis after inclusion of 10 patients was planned to report adverse events and assess the safety profile. Since altogether only eight patients were included into the study, the ISMB evaluated the safety data once. In addition safety information was compiled in four Annual Safety Reports (January 2008 – December 2012). Neither safety information assessments nor changes in the SMPC or IB, deemed non-substantial, lead to changes in the positive risk-benefit evaluation of the study by the ISMB. In case of occurrence of another epileptic seizure, however, the present safety assessment would have been estimated as critically compromised by the ISMB.

Adverse Events (AE):

A total of 85 AEs (SAEs exclusive) were reported in the eight included patients throughout the time of the study. 76 AEs (89%) were mild reactions (Grade 1 toxicity: 53 AEs [62%], Grade 2 toxicity: 23 AEs [27%]). Nine AEs were of moderate Grade 3 toxicity (11%). There was no AE of Grade 4 toxicity. The AEs of grade 3 toxicity included anaemia (1), asthenia (1), diplopia (1), increase of gamma-glutamyltransferase (1), deterioration of general physical health (1), hyperkalaemia (1), pyrexia (1) and thrombocytopenia (2).

There was a median number of 6 AEs per patient with a minimum of 4 AEs (01/00001) and a maximum of 23 AEs (07/00001) per patient documented in the CRF.

The most frequent AEs in our patient cohort included headache (5), peripheral oedema (5), leukopenia (4), thrombocytopenia (4), diarrhoea (4), hyperkalemia (4), nasopharyngitis (3), hypercholesterolaemia (3) and hypertriglyceridaemia (3). All AEs were either mild or moderate severe reactions.

Serious adverse events (SAE):

A total of four SAEs were reported in four patients throughout the time of the study. The four reported SAEs were all of moderate Grade 3 toxicity. Two of the four documented SAEs (pyrexia and herpes zoster) were classified as possibly related to the intake of EVEROLIMUS (see 9.2.2.1). For the other two SAEs (epilepsy and hypersensitivity) a relationship with EVEROLIMUS maintenance was ruled out. All four SAEs resolved without sequelae. The two SAEs assessed as possibly study drug related are not unexpected adverse reactions. In fact pyrexia and infections are typical side effects of rapamycin derivatives due to their immunosuppressive properties

Suspected Serious Adverse Reactions (SARs):

A total of two SARs had to reported in the course of this study, see above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

The sponsor's assessment of expectedness was determined by referring to the IBs and

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin Prof. Dr. med. Peter Henningsen, Dekan
Name of Finished Product: Afinitor®
Name of Active Ingredient: EVEROLIMUS (RAD001)
SMPCs and no SUSARs have been reported in the study. [The Ethics Committee was, however, informed on SUSARs in relation EVEROLIMUS which were reported to Novartis Pharma AG by other institutions during the time the study]. **Summary of Adverse Events:** AEs documented during the course of our study comprise adverse reactions typically induced by the study drug and most AEs were mild in nature. The frequency of AEs was in the expected range regarding the morbidity of the patient collective enrolled into the study. Notably none of the patients in our study suffered non-infectious pneumonitis, a known class effect of rapamycin derivatives. **Surrogate parameters** Since surrogate parameters involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement could have been collected only in patients with these characteristics and we did not have such a case, this analysis was not applicable. **Overall Conclusion:** Due to the small number of eight patients included in this clinical trial, our study can only be considered as a pilot investigation without the power to draw statistical conclusions. Since frequency and severity of observed AE were in the expected range, it can nevertheless be concluded that a maintenance therapy with EVEROLIMUS is safe in patients with MCL having received disease control after one or two lines of chemotherapy and not being eligible for intensive chemotherapy regimens. Regarding feasibility we observed in our small cohort a high proportion of patients prematurely discontinuing study medication on personal request. So obviously the occurring AEs together with the subjective perceived deterioration of general health status and quality of life during continuous medication with EVEROLIMUS were unacceptable for many patients, especially as they were in a maintenance setting, knowing their disease controlled. Overall we come to the conclusion that EVEROLIMUS is not a satisfactory option for a continuous maintenance concept in our patient collective, but as EVEROLIMUS can be safely applied there is potential for combination with chemotherapy regimens in the future.
Date of the report: 10/02/2013
Date: **Signature LKP:**
Date: **Signature Statistician:**
Date: **Signature Co-Author**

Ethics and Good Clinical Practice

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC), and with the ethical principles laid down in the Declaration of Helsinki.

1 Introduction

1.1 EVEROLIMUS

EVEROLIMUS (RAD001, Afinitor®) has been in clinical development since 1996 for patients undergoing solid organ transplantation. The drug has been approved in several countries, including the majority of European Union states, as prophylaxis to prevent rejection in patients following renal and cardiac transplantation in combination with cyclosporine A and glucocorticosteroids. Its first commercialization in Germany (as Certican®) dates from March 2004.

Clinical development for oncology indications entered EVEROLIMUS in 2002. Afinitor was granted approval in the United States on 03/30/2009 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. Afinitor was approved by the European Commission on 08/03/09. Since 08/04/10, Afinitor is also approved in Argentina, Australia, Brazil, Canada, Chile, Columbia, Costa Rica, Guatemala, Hong Kong, Iceland, India, Indonesia, Israel, Japan, Lebanon, Macedonia, Malaysia, Mexico, New Zealand, Norway, Russia, Singapore, South Korea, Switzerland, Syria, Taiwan, Uruguay and Venezuela. Applications are pending in various other countries worldwide. At weekly and daily schedules and at various doses explored, EVEROLIMUS is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with EVEROLIMUS therapy are manageable. Non-infectious pneumonitis has been reported with mammalian target of rapamycin (mTOR) inhibitors but is commonly low-grade and reversible.

EVEROLIMUS is a novel macrolide derivative of rapamycin formulated for oral administration, which is being developed as an antiproliferative drug with applications as an immunosuppressant and anticancer agent.

At the cellular or molecular level, EVEROLIMUS has the same mechanism of action as an immunosuppressant or as an anti-tumor agent. It acts by selectively inhibiting mTOR, an intracellular protein kinase implicated in the control of cellular proliferation of activated T-lymphocytes or neoplastic cells. TOR is a ubiquitous protein kinase implicated in cell cycle control and specifically in the progression of cells from the G1- to S-phase. TOR is considered to be a downstream component of the PI3K/Akt pathway, its own primary downstream substrates being the eIF-4E-binding protein (4E-BP1) and p70 S6 kinase 1 (S6K1) which both play a role in the translational regulation of mRNAs encoding proteins involved in G1-phase progression. In this context, there is an increasing body of evidence suggesting that Akt regulates mTOR activity, and that the activation status of the PI3K/Akt pathway may be indicative for responsiveness to rapamycin derivatives such as EVEROLIMUS [Krymskaya, 2003; Bjornsti, 2004; Majumder, 2004; Panwalkar, 2004].

EVEROLIMUS acts on interleukin- and growth factor-dependent proliferation of cells through high affinity for an intracellular receptor protein, the immunophilin FKBP-12. The resulting FKBP-12/EVEROLIMUS complex then binds with mTOR to inhibit downstream signaling events.

1.2 Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a well-characterized subtype of B cell Non-Hodgkin lymphoma (B-NHL). The genetic hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32) leading to deregulation and up-regulation of Cyclin D1, an important regulator of the G1-phase of the cell cycle. This genetic event is present in basically all cases of MCL, but additional genetic alterations involving e. g. a dysregulated DNA-damage response have been described [Weisenburger, 1987; Fernandez, 2005].

Due to the chromosomal translocation t(11;14)(q13;q32) characteristic for MCL leading to deregulation and upregulation of Cyclin D1, Cyclin D1 mRNA is constitutively expressed in MCL. Cyclin D1 is a potential subject to translational regulation by a pathway involving the mammalian target of rapamycin (mTOR) [Bjornsti 2004; Hay, 2004]. Since elevated levels of Cyclin D1 expression in MCL cells may accelerate G1/S-phase transition and therefore tumor cell proliferation [Fernandez 2005], targeting the mTOR pathway is an attractive therapeutic approach in MCL.

mTOR is a downstream effector of the PI3K/Akt-signaling pathway. This pathway is frequently dysregulated in cancer cells [Shayesteh, 1999]. A recent report suggests that constitutive activation of the PI3K/Akt pathway contributes to the pathogenesis of MCL. Inhibition of the PI3K/Akt pathway in the MCL cell lines leads to cell cycle arrest and apoptosis [Rudelius, 2006].

1.3 Rationale for this study

Patients with MCL are typically older adults and usually present with stage IV disease. Response to chemotherapy usually results in a tumor response but remissions are short and the median survival is three to four years. There are several induction immunochemotherapy regimens for MCL. First, standard doxorubicin-containing regimens such as Rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Secondly, purine analogue-based regimens such as Rituximab-FCM (fludarabine, cyclophophamide and mitoxantrone) and, thirdly, intensive combination regimens including anti-metabolites such as Rituximab-Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with high-dose methotrexate and cytarabine. These regimens usually produce an 80-95% response rate with 34-87% complete responses [Lenz, 2004; Romaguera, 2005; Witzig, 2005a; Forstpointner, 2006]. The purine nucleoside analogues (e. g. Fludarabine, 2-Chlorodeoxyadenosine) show activity as single agents as well as in combination with Rituximab as do single-agent bortezomib, the combination of thalidomide and Rituximab, and single-agent temsirolimus [Witzig, 2005b].

The addition of high-dose chemotherapy or the combination of chemotherapy and radiation followed by autologous stem cell rescue results in an improvement of event free survival and probably overall survival [Gianni, 2003; Lefrere, 2004; Lenz 2004; Mangel, 2004; Dreyling, 2005; Witzig, 2005a]. However, this approach is reserved for patients eligible for stem cell transplantation (SCT), and none of these approaches can definitively cure patients with MCL [Witzig, 2005a]. Therefore, new agents and treatment options are urgently needed, especially

for elderly patients and patients not eligible for consolidation high-dose chemotherapy with autologous stem cell rescue.

As promising strategy to prolong disease free survival for elderly patients emerged the maintenance setting. Maintenance with interferon-α (IFN-α) was effective in advanced low-grade lymphomas, especially follicular lymphoma (FL), albeit associated with frequent side effects [Hiddemann, 1998]. Since maintenance with the Anti-CD20 mAb Rituximab had significantly prolonged response duration in patients with recurring or refractory FL and MCL [Forstpointner 2006], it seemed to be a promising alternative for further investigations. In the large prospective randomized European MCL Elderly trial the first randomization comparing two different induction regimens showed that R-CHOP is superior to R-FC, while a second randomization showed that maintenance therapy with Rituximab significantly improved both remission duration and overall survival at four years for patients responding to R-CHOP but not after R-FC [Kluin-Nelemans, 2012]. Based on these data bimonthly administration of Rituximab as maintenance therapy until relapse, is currently considered to be the new standard for elderly patients with MCL after R-CHOP induction [Witzens-Harig, 2012; Li, 2013].

As mentioned above inhibition of the PI3K/Akt signaling pathway by using mTOR inhibitors emerged as attractive strategy for treatment of MCL. Due to convincing results regarding overall response rate and progression free survival in several clinical trials, including one prospective, randomized Phase III trial, the mTOR inhibitor temsirolimus recently got approval for the treatment of relapsed or refractory MCL in the EU [Witzig 2005b; Ansell, 2008; Hess, 2009].

Recently several clinical trials have shown preliminary efficacy of EVEROLIMUS as single agent in patients suffering from a broad range of aggressive subtypes of relapsed B-NHL, including MCL [Tobinai, 2010; Witzig, 2011; Renner, 2012]. These promising results justify further evaluation, especially in a maintenance setting where response to the previous therapy is presumably short.

In summary, for patients not eligible for intensive chemotherapy regimens, the mean duration of remission is in the range of 12 to 20 months after initial chemotherapy. The results of chemotherapy are even worse in second, third and fourth line chemotherapies. Therefore, strategies to prolong remission duration in elderly patients with MCL are urgently needed. The effects of rapamycin derivates on MCL cells *in vitro* and the evolving *in vivo* data support the further investigation of EVEROLIMUS in this incurable disease.

2 Study objectives

The current study aimed at evaluating the therapeutic potential of EVEROLIMUS (RAD001, Afinitor®) by analyzing the time to progression despite maintenance therapy with EVEROLIMUS.

Secondary aims included analysis of toxicity and feasibility of a treatment with EVEROLIMUS in patients with MCL after first, second, third and fourth line chemotherapy, a comparison of the duration of previous responses with the duration of responses in patients under maintenance therapy, analysis of the conversion rate in MCL patients during maintenance therapy (improvement of partial to complete response, stable disease to partial or complete response), an analysis of the overall survival of patients with maintenance therapy and an analysis of the Quality of life during maintenance therapy.

3 Investigational plan

3.1 Overall study design

This was an Investigator-initiated open-label, non-randomized, single-arm, multicentric (5-10 centers) Phase II trial with the mTOR-inhibitor EVEROLIMUS at 5 mg/d as maintenance therapy in patients with MCL aged over 60 years or aged over 40 years but who were not eligible for high-dose chemotherapy followed by autologous stem cell support or allogeneic stem cell transplantation. Treatment should be continued until disease progression.

It was planned to include 25 patients.

3.2 Discussion of design

This was a multi-center descriptive study to gain insight into potential efficacy and safety of a maintenance therapy with EVEROLIMUS in patients with MCL. Due to slower than expected recruitment, the study was prematurely terminated after having included only 8 patients.

Thus, it must be noted that data can only be described on a case base without being able to draw any general conclusions.

3.3 Study population

The sample consisted of eight patients with a proven history of mantle cell lymphoma.

3.3.1 Inclusion and exclusion criteria

Inclusion Criteria:

1. Patients with a proven history of mantle cell lymphoma
2. Patients with achieved disease control after one to four lines of chemotherapy (complete response, partial response, stable disease) for mantle cell lymphoma
3. Patients must have been treated with a CHOP-like chemotherapy or a Fludarabine-containing regimen previously and Rituximab must have been used as part of the previous treatment
4. Age ≥60 years or patients ≥40 and <60 years of age who are not eligible for high-dose chemotherapy followed by autologous stem cell support or allogeneic stem cell transplantation
5. Minimum of two weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy)
6. WHO performance status ≤2
7. Adequate bone marrow function as shown by:
   ANC ≥1.5 x 10^9/L, Platelets ≥100 x 10^9/L, Hb >9 g/dL
8. Adequate liver function as shown by: serum bilirubin ≤1.5 x upper limit of normal (ULN), and serum transaminases activity ≤3 x ULN. With the exception of serum transaminases (<5 x ULN) if the patient has liver metastases
9. Life expectancy of at least 3 months

10. Signed informed consent

Exclusion Criteria:

1. Prior treatment with any investigational drug within the preceding 4 weeks
2. Chronic treatment with systemic steroids or another immunosuppressive agent except for Rituximab
3. Uncontrolled brain or leptomeningeal disease manifestation, including patients who continue to require glucocorticoids for brain or leptomeningeal disease manifestation
4. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin
5. Other concurrent severe and/or uncontrolled medical disease which could compromise participation in the study (i. e., uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, unstable angina, or congestive heart failure - New York Heart Association Class III or IV, ventricular arrhythmias active ischemic heart disease, myocardial infarction within six months, chronic liver or renal disease, active upper GI tract ulceration, psychiatric disease)
6. A known history of HIV seropositivity
7. History or serology indicating active or chronic Hepatitis B or C or detection of viral DNA (Hep B or C) via PCR
8. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of EVEROLIMUS (e. g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
9. Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumarin)
10. Previous organ transplantation
11. Women who are pregnant or breast feeding, or women able to conceive and unwilling to practice an effective method of birth control. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of EVEROLIMUS). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. A highly effective method of birth control is defined as those which results in a low failure rate (i.e. less than 1% per year) for example sexual abstinence or vasectomized partner
12. Patients who have received prior treatment with an mTor inhibitor
13. History of noncompliance to medical regimens
14. Patients unwilling to or unable to comply with the protocol
15. Patients with galactose intolerance, lack of lactase or malabsorption of glucose or galactose

3.3.2 Interruption or discontinuation of treatment

For patients who were unable to tolerate the protocol-specified dosing schedule, dose adjustments were permitted in order to keep the patient on study drug. If administration of EVEROLIMUS had to be interrupted due to unacceptable toxicities, drug dosing was interrupted or modified according to a predefined algorithm for discontinuation of treatment described in the clinical study protocol. Toxicity was assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, CTCAEv3.

Reasons that a patient had to discontinue study medication (=end of treatment) were one of the following:

- Suspected Unexpected Serious Adverse Reaction
- abnormal laboratory value(s) according to 3.2.3 Interruption or discontinuation of treatment, Table 1 in the study protocol
- personal request to stop medication
- doctor´s request

Reasons that a patient had to discontinue participation in the clinical study (=end of study) were considered to constitute one of the following:

- disease progression
- protocol violation
- subject withdrew consent
- lost to follow-up
- administrative problems
- death

3.4 Treatments

3.4.1 Investigational therapy

The investigational therapy used in the course of this study was EVEROLIMUS. Study medication had to be taken by the patients themselves. During the study, EVEROLIMUS was administered orally as one daily dose of 5mg (1 x 5 mg tablets) continuously from study day 1 until disease progression or occurrence of toxicity that was not manageable by EVEROLIMUS interruption or dose reduction to 2.5 mg EVEROLIMUS per day as described in the protocol (EVEROLIMUS was available as tablets for oral administration as tablets containing 2.5 mg or 5 mg strength of active substance).
The study drugs were supplied by Novartis to the pharmacy of Klinikum rechts der Isar and distributed to the study centers by the pharmacy.

3.4.2 Treatment assignment

Tablets were blister-packed under aluminum foil in units of ten tablets, which should be opened only at the time of administration as the drug is hygroscopic and light-sensitive.

EVEROLIMUS should be taken by the patient in the morning as a single dose in a fasting state or with no more than a light fat-free meal. Dietary habits around the time of EVEROLIMUS intake should be as consistent as possible throughout the study.

3.4.3 Blinding

Not applicable.

3.4.4 Concomitant therapy

Patients were instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications having been taken within 30 days of screening should be recorded. If concomitant therapy had to be added or changed, the reason and name of the drug/therapy had to be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient was allowed, including drugs given prophylactically (e. g. antiemetics +/- steroids), with the following exceptions:

- no other investigational therapy should be given to patients
- no chronic treatment with systemic steroids or another immunosuppressive agent (except for Rituximab)
- no anticancer agents other than the study medications administered as part of the described study protocol should be given to patients (except for Rituximab). If such agents were required for a patient then the patient had to be first withdrawn from the study
- leukocyte growth factors (e. g. G-CSF and GM-CSF) were not to be administered systematically but could be prescribed by the investigator for severe neutropenia if this was thought to be appropriate
- drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided in association with EVEROLIMUS as these can alter metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A should not be administered as systemic therapy (see study protocol for prohibited medications)

The investigator had to instruct the patient to notify the study staff about any new medications he/she was taking after the start of the study drug. All medications (other than study drug/s) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient started treatment with study drug had to be recorded.
The use of Rituximab maintenance therapy was allowed and up to the discretion of the treating physician.

3.4.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits were kept during the study. Drug accountability was noted by the field monitor during site visits and at the completion of the trial. Patients were asked to return all unused medication at the end of the study.

3.5 Visit schedule and assessments

0 lists all of the assessments and indicates the visits when they were performed with an “X”. Patients should have been seen for all visits on the designated day or as close to it as possible. All data obtained from the assessments listed in 0were to be supported in the patient’s source documentation.

3.5.1 Visit schedule

Table 1 Visit Schedule

Examination	Screening	Baseline	Week			Month				
	-14 to -7 Days	Day 0	1	2	4	2	3	6	Every three months	EOS / 24 months
Informed consent	X									
Medical History	X									
Inclusion/exclusion criteria	X									
Vital signs		X	X	X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X	X	X
ECG	X						X			X
CT[1)2)]		X					X	X	X	X
Bone Marrow Assessment [1), 3)]		(X)					(X)	(X)	(X)	(X)
Esophagogastro-duodenoscopy[4,]		(X)					(X)	(X)	(X)	(X)
Laboratory test	X	X	X	X	X	X	X	X	X	X
Quality of life	X	X					X	X	X	X
Analysis of surrogate parameters[5)]		(X)					(X)	(X)	(X)	(X)

[1)] immediately in case of suspected progression
[2)]a chest x-ray and an abdominal sonography could be performed alternatively

[3)]Bone marrow assessment had to be done during follow up exclusively in case of initial bone marrow involvement
[4)]Esophagogstroduodenoscopy had to be performed exclusively in patients with proven gastrointestinal lesions if clinically indicated

[5)]surrogate parameters had to be taken exclusively from patients with circulating MCL cells or with bone marrow involvement

In the case of “end of treatment” an additional “end of treatment visit” had to be performed as indicated below. Afterwards there was a short follow-up every three months until a modified “end of study visit” had to be performed.

Table 2 Evaluation and visit schedule in case of end of treatment before 24 months

Examination	End of treatm.	Every three months	EOS / 24 months
Vital signs	X	X	X
Physical examination	X	X	X
ECG	X		X
CT[1)2)]	X	X	X
Bone Marrow Assessment [1), 3)]	(X)	(X)	(X)
Esophagogastro-duodenoscopy[4)]	(X)	(X)	(X)
Laboratory test	X	X	X
Quality of life	X		X
Analysis of surrogate parameters[5)]	X		

[1)] immediately in case of suspected progression
[2)] a chest x-ray and an abdominal sonography could be performed alternatively
[3)] Bone marrow assessment had to be done during the three months follow-ups only if clinically indicated
[4)] Esophagogstroduodenoscopy had to be performed exclusively in patients with proven gastrointestinal lesions if clinically indicated
[5)]surrogate parameters had to be taken exclusively from patients with circulating MCL cells or with bone marrow involvement

All eight patients in our study were included while version 2.0 was the current version of the study protocol. Since this version did not differentiate between active treatment period and observation period after having finished study medication, (after discontinuation of maintenance therapy with EVEROLIMUS) the visit schedule remained the same as under treatment.

3.5.2 Efficacy assessments

3.5.2.1 Efficacy variables

Efficacy was measured by time to progression, overall survival and quality of life despite maintenance therapy with EVEROLIMUS. The last day of remission-inducing chemotherapy was defined as the first day of measurement. Efficacy was measured by the listed diagnostic measures (CT scan or chest X-ray and abdominal sonography; if clinically indicated esophagogastroduodenoscopy could be performed).

3.5.2.2 Criteria for assessing efficacy

A modification of the recommendations of an International workshop to standardize response criteria for Non-Hodgkin lymphoma was applied [Cheson 1999]. Response criteria were defined as follows:

Complete remission (CR):

CR was defined as complete disappearance of all objective signs of disease including enlarged lymph nodes, as well as hepatomegaly and splenomegaly. In case of improvement of response during the study period, CR had to be documented for at least a period of two months. In case of bone marrow involvement, clearance of bone marrow by lymphoma had to be documented by bone marrow biopsy and normalization of blood counts.

Undocumented complete remission (CRu):

CRu was defined as the disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities and normalization of the performance status. If persisting lymphoma cells were detected in any puncture or biopsy, the response was defined as partial remission (PR). Similar to CR, CRu had to be documented for a period of at least two months after end of therapy.

Partial remission (PR):

PR was defined as at least 50% reduction (≥50%) of all measurable and evaluable areas of lymphoma (sum of products of the largest diameters vertical to each other) for at least four weeks without occurrence of new manifestations, and normalization of blood count.

Stable disease (SD):

Tumor regression <50%, no new manifestations, and progression <25%.

Progression (PD):

Progressive disease was defined as:

- Increase of frequency and severity of symptoms
- New nodal manifestations of lymphoma

- Enlargement of manifestations of lymphoma more than 25%

Time to progression (TTP):
Interval between last day of application of remission-inducing chemotherapy to detection of progressive disease. Furthermore, the time period from start of maintenance therapy with EVEROLIMUS and detection of progressive disease had to be documented.

3.5.3 Safety assessments

Safety assessments consisted of monitoring and recording of all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs and the performance of physical examinations. These parameters should have been performed within ±3 days of the study visits except for adverse events that were evaluated continuously through the study. Safety and tolerability were assessed according to the NIH/NCI CTC (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

Patients were monitored in the outpatient department on week 1, 2 and 4 during the first month, on months 2, 3 and 6 and every 3 months thereafter. Patients were examined for signs of progressive disease.

3.5.4 Independent Safety Monitoring Board

A group of independent experts formed an independent Safety Monitoring Board (ISMB).

The ISMB independently reviewed the safety data during study duration. The board was to review the safety data at least once a year and in addition an interim analysis after inclusion of ten patients was planned to report about observed adverse events and to assess the safety profile.

3.5.5 Drug levels and pharmacokinetic assessments

Drug level assessment of EVEROLIMUS (RAD001; Afinitor®) was initially designated to be performed twice during study participation, for the first time during study visit in week one and later during study visit in month six. Analyses of EVEROLIMUS drug levels were not performed however. Since EVEROLIMUS had already been approved for the treatment of certain cases of advanced renal cell carcinoma by the time the amended protocol Version 4.0 was accepted, analyzing PK samples was not estimated necessary anymore. So obtainment of PK samples was eliminated from the evaluation and visit schedule in protocol Version 4.0.

4 Protocol amendments, other changes in study conduct

4.1 Protocol amendments

There were three protocol amendments:

The first amendment comprised changes in the protocol formulations as requested by the Ethics Committee before first approval of the study. On 03/20/2008 first approval of EC of protocol Version 2.0 was achieved. Due to recruiting problems the second amendment (V.3.0 of the study protocol of 09/01/2010 was approved by the EC 10/25/2010) comprised: enlargement of the patient population from first and second line patients also to third and

fourth line patients. For the same reason the third amendment (approved by EC: 09/ 07/2011) reduced the patient number from 35 to 25. In V.4.0 important new data on the study drug was reported and the visit schedule and statistical analysis was changed since e. g. pharmacokinetic assessments were not necessary anymore since enough data of this were available (see above). A differentiation between end of treatment and end of study was made since e. g. a clear follow-up phase in case of early withdrawal from study medication had not been defined before.

All eight patients included into the clinical trial were included under protocol version 2.0. Analysis of the patient population has been performed following the actual protocol version since this version consists in an amelioration and precision of the older versions.

4.2 Other changes in study conduct

The patient informed consent had been changed once in 2011 in order to reflect new safety information for EVEROLIMUS (approved by EC: 04/21/11).

In 2012 it was decided to close the clinical study prematurely, because it had been demonstrated over the course of the study, that even the changed recruitment rate for protocol V4.0, 25 patients (under V.2.0 it was planned to include 35 patients into the clinical trial), could not be kept (e. g. other competing studies, new medications slowed enrollment of the patients).

5 Data management

5.1 Data collection

Designated investigator staff entered the information required by the protocol into Case Report Forms (CRF) that were printed on paper. Field monitors reviewed the CRF for completeness and accuracy, and instructed site personnel to make any required corrections or additions. The CRF were forwarded to the MSZ by the investigational site, one copy being retained at the investigational site. Once the CRF were received, their receipt was recorded, and they were forwarded to the responsible data management staff for processing.

5.2 Database management and quality control

Data items from the CRF were entered centrally into the study database by MSZ staff using double data entry with verification upon second entry. Text items (e. g. comments) were entered once and checked manually against the CRFs. Adverse Events and SAEs were coded using the Medical dictionary for regulatory activities (MedDRA) terminology. When the database was declared to be complete and accurate, the database was locked. Any changes to the database after that time could only be made by joint written agreement between the Coordinating Investigator and the MSZ.

6 Statistical methods

6.1 Statistical methods

Data was summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements.

Primary efficacy endpoint was planned to be analyzed using 95% confidence intervals for the mean time to progression. The primary analysis was planned to be done separately for patients after first and second line of chemotherapy and ones after third and fourth line of chemotherapy.

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e. g.electrocardiogram, vital signs, special tests) were considered as appropriate.

Adverse events were planned to be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each body system and having each individual AE. Any other information collected (e. g. severity or relationship to study medication) will be listed as appropriate.

Due to the observational nature of the study and the total sample size of N=8 patients descriptive analyses of efficacy observations and measurements, safety observations and measurements were employed on a case base for all eight patients.

6.2 Interim Analyses

One interim analysis was intended to evaluate the safety of a maintenance therapy with EVEROLIMUS. This analysis was planned after having enrolled the first ten patients into the study. While awaiting the results of this interim safety analysis patient enrollment was planned to be continued. In addition, in case of an unexpected accumulation of serious adverse reactions other than those mentioned above, enrollment would have had to be put on hold.

Due to the observational character of the study and the small sample size of only eight patients no interim analysis was performed.

Primary outcome:

Time to progression (TTP) despite maintenance therapy with EVEROLIMUS

Secondary outcomes:

- Toxicity and feasibility of a treatment with EVEROLIMUS in patients with MCL after first, second, third and fourth line chemotherapy
- Surrogate parameters involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement (only in patients with circulating MCL cells or with bone marrow involvement)
- Comparison of the duration of previous responses with the duration of responses in patients with maintenance therapy
- Analysis of the conversion rate in MCL patients during maintenance therapy (improvement of partial to complete response, stable disease to partial or complete response)

- Overall survival of patients with maintenance therapy
- Quality of life during maintenance therapy

6.3 Populations

The **Safety Analyzable Population** (SAP) was planned to include all patients who received at least one dose of EVEROLIMUS.

The Intention to Treat (**ITT) Population** was planned to include all enrolled patients who received at least one dose of EVEROLIMUS. Patients who were going off study or discontinued treatment with study drug (end of treatment) due to AEs or toxicity prior to the key response evaluation were considered as having a progression at time of leaving the study.

The **Efficacy Analyzable Population** (EAP) was planned to consist of all patients who received EVEROLIMUS for at least four weeks and who did not violate inclusion or exclusion criteria.

Any patient in the ITT population who did not violate any of the inclusion or exclusion criteria and would be excluded from the efficacy analyzable population purely for having less than four weeks of treatment were to be included in the efficacy analyzable population as a treatment failure if discontinuation of study medication was related to lack of efficacy of EVEROLIMUS or to toxicity.

Replacements of patients who were not in the efficacy analyzable population were in general not foreseen. Patients could be replaced in individual cases after discussion between the sponsor-investigator and the investigators if a patient was felt not to provide sufficient information for the assessment of safety and efficacy of EVEROLIMUS.

6.3.1 Background and demographic characteristics

The demographics (age, sex, and race), diagnosis and extent of cancer disease history and baseline characteristics (performance status) were to be summarized for all patients enrolled. All other data were to be listed for all patients enrolled.

6.3.2 Concomitant therapy

The use of concomitant therapy deemed necessary for the care of the patient was allowed with the exception of other investigational therapy, chronic treatment with immunosuppressive agents, other anticancer agents than study medication (lead to withdrawal of the patient from the study) during participation of the study. Certain concomitant therapy should be avoided (e.g. due to interference with study medication; see Study Protocol Table 3).

6.3.3 Efficacy evaluation

Primary efficacy parameters

Efficacy was measured by time to progression, despite maintenance therapy with EVEROLIMUS. The last day of the remission-inducing chemotherapy was defined as the first day of measurement. Efficacy was measured by the listed diagnostic measures (CT scan or chest X-ray and abdominal sonography; if clinically indicated, esophagogastroduodenoscopy could be performed).

Secondary efficacy parameters
Efficacy was measured by overall survival and quality of life despite maintenance therapy with EVEROLIMUS.

6.3.3.1 Criteria for assessing efficacy

A modification of the recommendations of an International workshop to standardize response criteria for Non-Hodgkin lymphoma was applied [Cheson 1999]. Response criteria were defined as follows:

Complete remission (CR):

CR was defined as complete disappearance of all objective signs of disease including enlarged lymph nodes, as well as hepatomegaly and splenomegaly. In case of improvement of response during the study period, CR had to be documented for at least a period of 2 months. In case of bone marrow involvement, clearance of bone marrow by lymphoma had to be documented by bone marrow biopsy and normalization of blood counts.

Undocumented complete remission (CRu):

CRu was defined as the disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities and normalization of the performance status. If persisting lymphoma cells were detected in any puncture or biopsy, the response was defined as partial remission (PR). Similar to CR, CRu had to be documented for a period of at least 2 months after end of therapy.

Partial remission (PR):

PR was defined as at least 50% reduction (≥50%) of all measurable and evaluable areas of lymphoma (sum of products of the largest diameters vertical to each other) for at least 4 weeks without occurrence of new manifestations, and normalization of blood count.

Stable disease (SD):

Tumor regression <50%, no new manifestations, and progression <25%.

Progression (PD):

Progressive disease was defined as:

- increase of frequency and severity of symptoms
- new nodal manifestations of lymphoma
- enlargement of manifestations of lymphoma more than 25%

Time to progression (TTP):

Interval between last day of application of remission-inducing chemotherapy to detection of progressive disease. Furthermore, the time period from start of maintenance therapy with EVEROLIMUS and detection of progressive disease had to be documented.

6.3.4 Safety evaluation

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs and the performance of physical examinations.

These parameters had to be performed within ±3 days of the study visits except for adverse events that had to be evaluated continuously throughout the study. Safety and tolerability were assessed according to the NIH/NCI CTC http://ctep.cancer.gov/forms/CTCAEv3.pdf.

6.3.5 Interim analyses

Not applicable

6.3.6 Other topics

Not applicable

6.4 Sample size and power considerations

In protocol Version 2.0. 35 patients were planned to be included into the clinical trial since it started from the hypothesis that 40% instead of 20% of the patients could be observed without disease progression after two years. A total of 35 patients would have been needed to be treated to detect this difference with a power of 80% on one sided alpha level of 5%.

For the already stated slow recruitment the patient population was changed to also including more severely ill patients (not only first and second line patients could be included into the clinical trial, but also third and fourth line patients) in protocol Version 4.0. Furthermore the patient number was changed to an explorative number of 25.

6.5 Patients studied

All eight patients included into this clinical trial will be analyzed in a case by case descriptive way.

6.5.1 Patient disposition

In total eight adult patients with a proven history of mantle cell lymphoma (MCL) were included into the study (first patient [07/00001] included: 09/19/2008; last patient [01/00002] included: 10/19/2009 (See 0).

None of the eight patients who received study medication are still under maintenance therapy with EVEROLIMUS and none of them completed the designated maintenance period of 24 months. The longest duration of study therapy was 459 days (07/00002). Two patients had to stop EVEROLIMUS maintenance due to disease progression under study medication (documented disease progression 5.2 months [07/00001] and 5.6 months [06/00001] after start of medication). One patient had to be taken off study medication due to medication interaction with the anticonvulsant valproic acid after having suffered an epileptic seizure (01/00001: 0.6 months after start of medication). The other five patients, (01/00002, 06/00002, 07/00002, 07/00003 and 07/00004), prematurely stopped study medication on personal request, 0.83 - 15.3 months after start of maintenance therapy. For two patients other reasons for discontinuation of study drug were additionally documented in the CRF. One patient (07/00001) having been taken off study drug due to disease progression developed diplopia as first symptom of progressive disease. Thus for this patient diplopia was indicated as additional reason for discontinuation of EVEROLIMUS besides disease progression. One patient (06/00002) stopped study medication at his own discretion after

having developed extrasystoles and atrial fibrillation. He finally discontinued EVEROLIMUS maintenance on personal request due to the suffered atrial fibrillation, specified as “other reason”.

One patient (07/00001) died 9.7 months after inclusion into the study due to disease progression.

01/00001 was not able to continue maintenance therapy with EVEROLIMUS over more than 17 days because he suffered a SAE (epileptic seizure), without relation to study medication, and was put on the known inhibitor of isoenzyme CYP3A4 valproic acid as anticonvulsant, as described above.

01/00002 finished maintenance therapy after all in all 25 days of EVEROLIMUS intake on personal request. Only seven days after having started maintenance therapy 01/00002 had to pause EVEROLIMUS for 55 days due to Herpes zoster. After recovery from the infection he started maintenance therapy again, but finished participation in the study only 18 days later on personal request.

Table 3 Patient disposition

PatientID	Date of study inclusion	Start of maintenance with EVEROLIMUS	Discontinuation of EVEROLIMUS maintenance	Reason for discontinuation of study medication
01/00001	02/13/09	02/13/09	03/01/09	Anticonvulsive therapy with valproic acid (strong inhibitor of isoenzymeCYP3A4)
01/00002	10/19/09	10/28/09	01/15/10	Personal Request
06/00001	07/23/09	08/06/09	02/02/10	Progressive Disease
06/00002	10/07/09	10/29/09	12/13/09	Personal Request due to extrasystoles, atrial fibrilation
07/00001	09/19/08	09/22/08	02/27/09	Progressive Disease and AE: diplopia
07/00002	10/07/08	10/08/08	01/12/10	Personal Request
07/00003	02/02/09	02/03/09	12/21/09	Personal Request
07/00004	06/17/09	06/18/09	08/26/09	Personal Request

For information on how dates from study entry to study determination (i.e. premature discontinuation of study medication) relate to scheduled visits according to the study scheme, please refer to 0 in chapter 3.5.1, where all conducted visits of the eight patients enrolled into the study are listed.

6.6 Baseline demographic and background characteristics

All in all eight adult patients with a proven history of mantle cell lymphoma (MCL) were included into the study (first patient [07/00001] included: 19.09.2008; last patient [01/00002] included: 19.10.2009. Patients were 63 – 80 years (median 73 years) of age and the male/female ratio was 7:1, which confirms a clear predominance of males vs. females suffering from MCL.

With one exception (06/00002; protocol deviation of inclusion criterion “achieved disease control after one or two lines of chemotherapy“ under Protocol V.2.0) patients had received one or two chemotherapy lines for MCL treatment before they were screened for participation in our study. Administered therapy schedules were basically CHOP, bendamustin or fludarabin-containing regimens and all patients had been exposed to Rituximab (0).

Table 4 Prior therapy lines

PatientID	Date of first diagnosis	Prior Chemotherapy	Therapy period	Date of study inclusion
01/00001	09/22/08	Vincristin, Prednisone (prephase treatment), Rituximab-CHOP	09/30/08 – 01/20/09	02/13/09
01/00002	04/09/09	Rituximab-CHOP	05/12/09 – 08/25/09	10/19/09
06/00001	09/27/07	Chlorambucil	09/26/07 – 10/25/07	07/23/09
		Rituximab-Bendamustin	01/22/09 – 03/24/09	
06/00002	06/20/03	Rituximab-CHOP	01/15/04 – 05/15/04	10/07/09
		Rituximab-FC	12/06/06 – 02/09/07	
		Rituximab-Bendamustin	05/19/09 – 08/18/09	
07/00001	09/15/06	Rituximab-CHOP, MTX	10/25/06 – 05/15/07	09/19/08
		Cyclophosphamide, high-dose Cytarabine, Mitoxantrone	05/14/08 – 08/15/08	
07/00002	03/03/08	Rituximab-CHOP	04/07/08 – 09/15/08	10/07/08
07/00003	08/08/08	Rituximab-CHOP	08/21/08 – 12/02/08	02/02/09
07/00004	10/31/08	Rituximab-FC	12/03/08 – 05/07/09	06/17/09

6.7 Protocol deviations

Protocol deviations mainly concerned deviations in laboratory and ECG assessment (e. g. missing parameters, lacking imaging and QLQ assessments), and wrong timing in scheduled visits.

6.8 Groupings for analysis

6.8.1 Safety Analyzable Population

As all eight patients enrolled into the study were actually treated with EVEROLIMUS, all of them can be assigned to the **Safety Analyzable Population**.

6.8.2 ITT Population

As described above, the **ITT Population** includes all enrolled patients who received at least one dose of EVEROLIMUS and considers patients who were going off study or discontinued treatment with study drug (end of treatment) due to AEs or toxicity prior to the key response evaluation as having a progression at time of leaving the study.

Based on these criteria all eight patients could be assigned to the **ITT Population,** as all of them were treated with EVEROLIMUS. All six patients who stopped medication not due to progress would have to be treated as having a progression at time of end of treatment (see 0 Patient disposition).

6.8.3 Efficacy Analyzable Population

As described above, patients who received EVEROLIMUS for at least four weeks and who did not violate inclusion or exclusion criteria could be assigned to the **Efficacy Analyzable Population**. Two patients, 01/00001 and 01/00002, stopped maintenance with EVEROLIMUS after altogether less than four weeks on study medication.

As the occurrence of an epileptic seizure of patient 01/00002 was not rated as related to study drug, the stopping of study medication of this patient was not toxicity-related. Thus, patient 01/00001 is not to be considered as treatment failure in the **Efficacy Analyzable Population**. Patient 01/00002 stopped study treatment after a herpes zoster infection possibly related to study drug. Since in this case stopping of study medication of this patient was toxicity-related, this patient would have to be considered as treatment failure in the **Efficacy Analyzable Population.**

Two patients (06/00001 and 06/00002) were included violating inclusion or exclusion criteria. The remaining 4/8 Patients could be assigned to the **Efficacy Analyzable Population** consisting of all patients who received EVEROLIMUS for at least four weeks and who did not violate inclusion or exclusion criteria. The remaining two patients stopped maintenance with EVEROLIMUS after altogether less than four weeks on study medication (see 0).

Table 5 Overall grouping of patients in statistical analysis populations

Patient ID	Safety Analyzable Population	ITT Population	Efficacy Analyzable Population	Comments
01/00001	X	X	Medication for less than 4 weeks, treatment failure	Considered as having a progress at last day of study drug
01/00002	X	X	Medication for less than 4 weeks, treatment failure	Considered as having a progress at last day of study drug
06/00001	X	X		Protocol deviation in inclusion/exclusion criteria (Inclusion criterion platelets ≥ 100 x 10^9/L, 10^9/L not fulfilled)
06/00002	X	X		Protocol deviation in inclusion/exclusion criteria (Inclusion criterion “achieved disease control after one or two lines of chemotherapy“ not fulfilled)
07/00001	X	X	X	
07/00002	X	X	X	
07/00003	X	X	X	
07/00004	X	X	X	

Due to the very small patient number of eight, patients were only theoretically grouped into the different analyzable populations. However, analysis could only be performed in a descriptive way for all patients on a case by case base.

7 Medication

7.1 Study medication

The investigational therapy used in the course of the present study was EVEROLIMUS (RAD001; Afinitor®).

7.1.1 Dosage

During the study EVEROLIMUS was administered orally as a single daily dose of 5 mg (1x 5 mg tablets) continuously from study day 1 until documented disease progression or occurrence of toxicity that could not be managed by temporary interruption of study medication or dose reduction to 2.5 mg EVEROLIMUS per day.

7.1.2 Patient exposure

EVEROLIMUS study medication was administered by the patients themselves. During the study EVEROLIMUS was administered orally as once daily dose of 5 mg (1 x 5 mg tablets) continuously from study day 1 until progression of disease or occurrence of toxicity that was not manageable by EVEROLIMUS interruption or dose reduction to 2.5 mg EVEROLIMUS per day as described in the protocol.

None of the eight patients who received the study medication concluded the intended 24 months of maintenance therapy with EVEROLIMUS. Longest duration of study therapy was 459 days (07/00002). Two patients discontinued study medication due to documented disease progression under study medication, One patient had to stop maintenance therapy due to known interactions between EVEROLIMUS and the anticonvulsant valproic acid after having suffered an epileptic seizure. The remaining five patients discontinued study medication on personal request. Patient 07/00001 stopped maintenance therapy due to progression and diplopia (probably also due to progression), 06/00002 stopped maintenance therapy on personal request due to extrasystoles and atrial fibrillation (see 0).

Table 6 Patient Exposure to study drug (EVEROLIMUS)

PatientID	EVERLIMUS Start Date	EVEROLIMUS End Date	Duration of therapy (days)	Dose (mg)	Dose Delay (days)	Reason for Dose Delay	Dose Adjustment
01/00001	02/13/09	03/01/09	17	5	no		no
01/00002	10/28/09	11/03/09	25	5	yes (55)	herpes zoster	no
	12/29/09	01/15/10		5	no		no
06/00001	08/06/09	02/02/10	181	5	no		no
06/00002	10/29/09	12/13/09	46	5	no		no
07/00001	09/22/08	02/27/09	159	5	no		no
07/00002	10/08/08	11/12/08	459	5	yes (3)	mucositis	no
	11/16/08	01/12/10		5	no		no
07/00003	02/03/09	12/21/09	322	5	no		no
07/00004	06/18/09	08/26/09	70	5	no		no

7.1.3 Drug level and pharmacokinetic data

Drug level assessment of EVEROLIMUS (RAD001; Afinitor®) was initially designated to be performed twice during study participation, for the first time during study visit in week one and later during study visit in month six. Since EVEROLIMUS had already been approved for the treatment of certain cases of advanced renal cell carcinoma by the time the amended protocol Version 4.0 was accepted, the collected PK samples for EVEROLIMUS drug levels was not estimated necessary anymore and obtainment of PK samples was eliminated from the evaluation and visit schedule in protocol Version 4.0.

7.2 Concomitant medication

The use of any concomitant medication/therapies deemed necessary for the care of the patient was allowed, including drugs given prophylactically (e. g. antiementics +/- steroids) with the following exceptions. No other investigational therapies, no chronic treatment with systemic steroids or other immunosuppressive agents (except for Rituximab) and no anticancer agents other than the study medication administered as part of the study protocol, except for rRituximab, were allowed during participation of the study.

Before therapy with another anticancer agent (except for Rituximab) could be started, the respective patient had to be withdrawn from the study first.
Leukocyte growth factors (e. g. G-CSF and GM-CSF) should not be administered systemically but could be prescribed by the investigator for severe neutropenia, if this was thought to be appropriate. Drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided in association with EVEROLIMUS as these could alter metabolism. A list of strong inducers and inhibitors of the isoenzyme CYP3A being prohibited as systemic therapy during participation in the study was provided in the study protocol. The investigator should instruct the patient to notify the study staff about any new medication he/she took after the start of the study drug.

8 Efficacy results

Efficacy had to be assessed by CT scan or chest X-ray and abdominal sonography. If clinically indicated esophagogastroduodenoscoy could be performed as well.

Due to the small patient number in the study (8 patients) we decided to present efficacy results of all patients having been treated in the study in a descriptive manner regardless of their classification in the different analysis-populations.

8.1 Time to progression (TTP)

5/8 Patients developed documented disease progression during the predefined observation period of two years. TTP in these patients, as defined in the study protocol (interval between last day of application of remission-inducing chemotherapy to detection of progressive disease), ranged from 4.7 months (142 days patient 06/00001; 193 days, patient 07/00001; 303 days, patient 06/00001; 721 days, patient 01/00001) to 25.6 months (767 days, patient 07/00002) see 0. The period from start of maintenance therapy with EVEROLIMUS and detection of progressive disease ranged from 2.3 months (70 days) to 24.8 months (744 days), see 0. The median TTP in our study cohort was 10.1 months (303 days) with a median

period from start of maintenance therapy with EVEROLIMUS to detection of progressive disease of 5.6 months (168 days).

Two of the remaining three patients (01/00002 and 07/00003) did not develop disease progression until the end of the protocol-defined observation period of two years after study enrollment (01/00002 documented SD; 07/00003 documented PR).

The remaining third patient (07/00004) was lost to follow-up before having completed the observation period of two years. Until the last documented contact with the respective patient 566 days (18.9 months) after the last day of remission-inducing chemotherapy or 524 days (17.5 months) after start of maintenance therapy with EVEROLIMUS respectively no PD was documented.

Table 7 Time to progression (TTP)

PatientID	Last day of remission-inducing chemotherapy	Detection of progressive disease	TTP (days)	TTP (months)
01/00001	01/20/09	01/11/11	721	24
01/00002	08/25/09	SD documented for >24 months	---	---
06/00001	03/ 24/09	01/21/10	303	10.1
06/00002	08/18/09	01/07/10	142	4.7
07/00001	08/15/08	02/24/09	193	6.4
07/00002	09/15/08	10/22/10	767	25.6
07/00003	12/02/08	PR documented after 767 days (25.6 months)	---	---
07/00004	05/07/09	Lost to Follow-up; no documented PD until 566 days (18.9 months) after last day of remission-inducing chemotherapy	---	---

Table 8 Time from start of EVEROLIMUS maintenance to disease progression

PatientID	Start of EVEROLIMUS maintenance therapy	Detection of progressive disease	TTP (days)	TTP (months)
01/00001	02/13/09	01/11/11	697	23.2
01/00002	10/28/09	SD documented for >24 months	---	---
06/00001	08/06/09	01/21/10	168	5.6
06/00002	10/29/09	01/07/10	70	2.3
07/00001	09/22/08	02/24/09	155	5.2
07/00002	10/08/08	10/22/10	744	24.8
07/00003	02/03/09	PR documented after 704 days (23.5 months)	---	---
07/00004	06/18/09	Lost to Follow-up; no documented PD 524 days (17.5 months) after start of maintenance with EVEROLIMUS	---	---

8.2 Overall survival

For overall survival status of the eight patients 24 months after inclusion into the study see 0. 1/8 patients died within two years after enrollment into the study. Patient 07/00001 died 290 days (9.7 months) after study inclusion and 129 days (4.3 months) after maintenance therapy with EVEROLIMUS had been stopped due to documented disease progression. Documented reason for death of the patient was disease progression. At time of death the patient did not take part in the study anymore.

One patient (07/00004) was lost to follow-up 615 days (20.5 months) after study inclusion. Thus we do not have any information about her survival beyond this date.

As no further follow-up beyond 24 months after study inclusion of the patients was foreseen in the study protocol, we do not have any information concerning patients' survival beyond two years after enrollment into the study.

Table 9 Overall survival

PatientID	Survival 24 months after study inclusion
01/00001	still alive
01/00002	still alive
06/00001	Lost to follow-up after progressive disease 182 days (6.1 months) after study inclusion
06/00002	Lost to follow-up after progressive disease 84 days (2.8 months) study inclusion
07/00001	dead (patient died 290 days [9.7 months] after study inclusion)
07/00002	still alive
07/00003	still alive
07/00004	Lost to follow-up 615 days (20.5 months) after study inclusion

8.3 Quality of life

For QOL patients had to fill in a questionnaire about their general health status and QOL during maintenance therapy. Value 1 of their rating was defined as very bad; value 7 was defined as very good.

Here we present on a case base the values patients rated the two questions "general health status" and "quality of life".

Patient 01/00001 was only 17 days on study drug. The patient did not fill in the QLQ.

Patient 01/00002 was 25 days on study drug with a long (55 days) dose delay (see 0). Under first treatment with EVEROLIMUS the patient had a decrease of health status and QOL, (5;5; to 3;3); after restart of treatment health status and QOL increased again from 4;4 to 5;5, so a QOL change due to medication could not be detected.

Patient 06/00001 had a decrease of health status and QOL from 6;6 to 5;5 between month 3 and month 6 of treatment.

Patient 06/00002 had a decrease of QOL; he started at the level of 4;4, under treatment he increased to 5;5, then decreased to 2;2 after end of study treatment due to PD.

Patient 07/00001 also had a decrease of health status and QOL under study treatment. He started at 5;5; under treatment he decreased to 3;4, then increased again to 5;5 and between month 3 and 6 after start of treatment decreased to 3;3 due to PD.

Patient 07/00002 showed improvement of health status and QOL from 5;5 to 6;6 under treatment (last questionnaire was filled in 12 months after start of treatment).

Patient 07/00003 had a decrease of health status and QOL from 5;5 to 4;3 after 10 months of treatment with EVEROLIMUS.

Patient 07/00004 had a decrease of health status and QOL from 4;5 to 1;1 on month 2 under treatment.

Thus, from seven patients, who filled in QOL questionnaires, one patient had a small improvement, one did not really change and five patients had a decrease in QOL and health status under study treatment with EVEROLIMUS.

8.4 Secondary efficacy results

8.4.1 Conversion rate

One of the secondary endpoints in the study protocol was the analysis of the conversion rate in MCL patients during maintenance therapy with EVEROLIMUS, which means improvement of partial to complete response or improvement of stable disease to partial or complete response.

In the following, the conversion of all eight patients is described on a case by case basis:

- Patient 01/00001 had no conversion under maintenance treatment
- Patient 01/00002 did not change in diagnosis SD from baseline to end of treatment
- Patient 06/00001 converted from SD to PD under maintenance treatment
- Patient 06/00002 converted from SD to PD under maintenance treatment
- Patient 07/00001 did not change in diagnosis SD under maintenance therapy
- Patient (07/00002) converted from PR at study inclusion to CR during maintenance therapy with EVEROLIMUS (after month 6)
- Patient 07/00003 did not change in diagnosis PR from month 3 to end of treatment 322 days after start of maintenance therapy
- Patient 07/00004 did not change in CR from baseline to end of treatment after 70 days of treatment.

Only one of eight patients underwent a positive conversion under maintenance therapy (07/00002), five patients stayed stable under maintenance therapy (01/00001; 01/00002; 07/00001; 07/00003; 07/00004). Two patients underwent a negative conversion from SD to PD (06/00001; 06/00002).

8.4.2 Comparison of the duration of previous responses with the duration of responses in patients with EVEROLIMUS maintenance therapy

This comparison is only feasible in patients who already underwent two lines of therapy before maintenance therapy. The date of detection of progress was not directly evaluated in

the CRF, so we present as “previous response” the end of first or second line therapy to start of the next chemotherapy (see 0).

Patient 06/00001 had a TTP of 455 days after first line chemotherapy and a TTP of 303 days from last day of remission-inducing chemotherapy to detection of progressive disease with EVEROLIMUS.

Patient 06/00002 had a TTP of 935 days after first line chemotherapy, a TTP of 830 days after second line chemotherapy and a TTP of 142 days from last day of remission-inducing chemotherapy to detection of progressive disease with EVEROLIMUS.

Patient 07/00001 had a TTP of 365 days after first line chemotherapy and a TTP of 193 days from last day of remission-inducing chemotherapy to detection of progressive disease with EVEROLIMUS.

Table 10 Comparison of duration of previous responses with duration of response with EVEROLIMUS

PatientID	End of 1st-line CTX	Start of 2nd-line CTX	TTP (d)	End of 2nd-line CTX	Start of 3rd-line CTX	TTP (d)	Last day of remission-inducing CTX	Detection of PD	TTP (d)
06/00001	10/25/07	01/22/09	455	---	---	---	03/24/09	01/21/10	303
06/00002	05/15/04	12/06/06	935	02/09/07	05/19/09	830	08/18/09	01/07/10	142
07/0001	05/15/07	05/14/08	365	---	---	---	08/15/08	02/24/09	193

8.5 Other topics

8.5.1 Surrogate parameters

Since surrogate parameters involved in angiogenesis and cell-cycle regulation in patients with circulating MCL cells or bone marrow involvement could have been collected only in patients with these characteristics this analysis was not applicable, since none of these patients were included into the study.

9 Safety results

Safety information collected included in addition to adverse events (AE), serious adverse events (SAE) and serious adverse reactions (SAR) data on performance status, the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs and the performance of physical examinations.

Details on the data that had to be collected are provided in the clinical study protocol (Clinical study protocol: 4.5 Safety assessments).
AEs were graded according to the NIH/NCI CTCAEv3.

Independent Safety Monitoring Board

A group of independent experts formed an Independent Safety Monitoring Board (ISMB).

The ISMB independently reviewed the safety data during study duration. The board was to review the safety data at least once a year and in addition an interim analysis after inclusion of ten patients was planned to report adverse events and assess the safety profile. Since altogether only eight patients were included into the study, the ISMB evaluated the safety data once. In addition safety information was compiled in four Annual Safety Reports (January 2008 – December 2012). Neither safety information assessments nor changes in the SMPC or IB, all deemed non-substantial, lead to changes in the positive risk-benefit evaluation of the study by the ISMB. In case of occurrence of another epileptic seizure, however, the present safety assessment would have been estimated as critically compromised by the ISMB.

9.1 Overall experience of adverse events (AEs)

Due to the small number of patients in our study we will not present AEs divided into different patient groups.

A total of 85 AEs (exclusive of SAEs) were reported in the eight included patients throughout the time of the study. 76 AEs (89%) were mild reactions (Grade 1 toxicity: 53 AEs [62%], Grade 2 toxicity: 23 AEs [27%]). Nine AEs were of moderate Grade 3 toxicity (11%). There was no AE of Grade 4 toxicity. The AEs of grade 3 toxicity included anaemia (1), asthenia (1), diplopia (1), increase of gamma-glutamyltransferase (1), deterioration of general physical health (1), hyperkalaemia (1), pyrexia (1) and thrombocytopenia (2).

There was a median number of 6 AEs per patient with a minimum of 4 AEs (01/00001) and a maximum of 23 AEs (07/00001) per patient documented in the CRF.

Very common adverse reactions during treatment with EVEROLIMUS include infections, anaemia, thrombocytopenia, headache, hypersensitivity, hyerglycaemia, hypercholesterolaemia, hypertriglyceridaemia, anorexia, dysgeusia, non-infectious pneumonitis, dyspnoe, epistaxis, cough, stomatitis, diarrhea, mucosal inflammation, vomiting, nausea, rash, fatigue, asthenia, peripheral oedema and pyrexia. More detailed information concerning adverse effects of EVEROLIMUS is provided in the Investigator's Brochure (IB).

The most frequent AEs in our patient cohort included headache (5), peripheral oedema (5), leukopenia (4), thrombocytopenia (4), diarrhoea (4), hyperkalemia (4), nasopharyngitis (3), hypercholesterolaemia (3) and hypertriglyceridaemia (3). All AEs were either mild or moderate severe reactions.

Thus in summary the AEs documented during the course of our study comprise adverse reactions typically induced by the study drug and most AEs were mild in nature. The frequency of AEs was in the expected range regarding the morbidity of the patient collective enrolled into the study. Notably none of the patients in our study suffered non-infectious pneumonitis, a known class effect of rapamycin derivatives.

0 presents an overview on documented AEs including information concerning severity. 0 provides a cumulative summary tabulation of all AEs sorted by affected organ classes. 0 presents a summary of AEs observed in each individual patient, including information regarding relation to study medication.

Table 11 Summary of documented AEs including severity (CTC grade)

Description of AE	Number of events	CTC grade 1/2	CTC grade 3/4
Abdominal pain upper	1	1	
Alanine aminotransferase increased	1	1	
Anaemia	2	1	1
Aphtous stomatitis	1	1	
Aspartate aminotransferase increased	2	2	
Asthenia	2	1	1
Atrial fibrillation	1	1	
Blood creatinine increased	2	2	
Blood glucose increased	1	1	
Blood urea increased	1	1	
Bronchitis	1	1	
Constipation	1	1	
Decreased appetite	2	2	
Diarrhoea	4	4	
Diplopia	1		1
Dysgeusia	1	1	
Dyspnoea	1	1	
Epistaxis	1	1	
Eye irritation	1	1	
Fatigue	2	2	
Freezing phenomenon	1	1	
Gamma-glutamyltransferase increased	2	1	1
General physical health deterioration	1		1
Haematoma	1	1	
Haemothorax	1	1	
Headache	5	5	
Hypercholesterolaemia	3	3	
Hyperkalaemia	4	3	1
Hypertriglyceridaemia	3	3	
Hypocalcaemia	2	2	
Impaired healing	1	1	
Leukopenia	4	4	
Malaise	1	1	
Medical device removal	1	1	
Mucosal inflammation	1	1	
Muscle spasms	1	1	
Musculoskeletal discomfort	1	1	
Musculoskeletal pain	2	2	
Nasopharyngitis	3	3	
Neck pain	2	2	
Neuropathy peripheral	1	1	
Oedema peripheral	5	5	
Pleural effusion	1	1	
Pyrexia	1		1
Rash	1	1	
Swelling	1	1	
Thrombocytopenia	4	2	2
Tinnitus	1	1	
Tongue ulceration	1	1	

Table 12 Cumulative summary tabulation of all AEs sorted by organ class

Blood and lymphatic system disorders	**10**
Anaemia	2
Leukopenia	4
Thrombocytopenia	4
Cardiac disorders	**1**
Atrial fibrillation	1
Ear and labyrinth disorders	**1**
Tinnitus	1
Eye disorders	**2**
Diplopia	1
Eye irritation	1
Gastrointestinal disorders	**8**
Abdominal pain upper	1
Aphtous stomatitis	1
Constipation	1
Diarrhoea	4
Tongue ulceration	1
General disorders and administration site conditions	**15**
Asthenia	2
Fatigue	2
General physical health deterioration	1
Impaired healing	1
Malaise	1
Mucosal inflammation	1
Oedema peripheral	5
Pyrexia	1
Swelling	1
Infections and infestations	**4**
Bronchitis	1
Naspharyngitis	3
Investigatons	**9**
Alanine aminotransferase increased	1
Aspartate aminotransferase increased	2
Blood creatinine increased	2
Blood glucose increased	1
Blood urea increased	1
Gamma-glutamyltransferase increased	2
Metabolism and nutrition disorders	**14**
Decreased appetite	2
Hypercholesterolaemia	3
Hyperkalaemia	4
Hypertriglyceridaemia	3
Hypocaclaemia	2
Musculoskeletal and connective tissue disorders	**6**
Muscle spasms	1
Musculoskeletal discomfort	1
Musculoskeletal pain	2
Neck pain	2
Nervous system disorders	**8**
Dysgeusia	1
Freezing phenomenon	1
Headache	5

Neuropathy peripheral	1
Respiratory, thoracic and mediastinal disorders	**4**
Dyspnoea	1
Epistaxis	1
Haemothorax	1
Pleural effusion	1
Skin and subcutaneous tissue disorders	**1**
Rash	1
Surgical and medical procedures	**1**
Medical device removal	1
Vascular disorders	**1**
Haematoma	1

Table 13 Summary of AEs observed in each individual patient including relation to study medication

PatientID	Description of AE	CTC-Grade	Relation to study drug
01/00001	Alanine aminotransferase increased	1	Possible
	Aspartate aminotransferase increased	1	Possible
	Neck pain	1	Unrelated
	Swelling	2	Unrelated
01/00002	Blood creatinine increased	1	Possible
	Blood urea increased	1	Possible
	Leukopenia	2	Possible
	Nasopharygitis	1	Unrelated
	Oedema peripheral	1	Unrelated
	Thrombocytopenia	3	Probable
06/00001	Haematoma	1	Possible
	Muskuloskeletal discomfort	2	Unrelated
	Oedema peripheral	1	Possible
	Thrombocytopenia	3	Possible
	Tinnitus	2	Possible
	Tongue ulceration	1	Possible
06/00002	Atrial fibrillation	2	Probable
	Blood glucose increased	1	Probable
	Decreased appetite	1	Possible
	Diarrhoea	2	Possible
	Fatigue	2	Possible
	Oedema peripheral	1	Possible
07/00001	Anaemia	3	Possible
	Aspartate aminotransferase increased	1	Possible
	Asthenia	3	Probable
	Blood creatinine increased	1	Unrelated
	Diarrhoea	1	Unrelated
	Diarrhoea	2	Probable
	Diplopia	3	Unrelated
	Dysgeusia	1	Probable
	Dyspnoea	1	Unrelated
	Fatigue	1	Unrelated
	Gamma-glutamyltransferase increased	1	Unrelated
	Gamma-glutamyltransferase increased	3	Possible

	General physical health deterioration	3	Unrelated
	Haemothorax	2	Unrelated
	Hypercholesterolaemia	1	Probable
	Hyperkalaemia	1	Possible
	Hyperkalaemia	3	Unrelated
	Hypertriglyceridaemia	1	Unrelated
	Hypocalcaemia	2	Unrelated
	Leukopenia	1	Probable
	Oedema peripheral	1	Unrelated
	Pleural effusion	1	Unrelated
	Thrombocytopenia	1	Probable
07/00002	Abdominal pain upper	1	Possible
	Aphtous stomatitis	2	Definite
	Bronchitis	2	Possible
	Diarrhoea	1	Probable
	Epistaxis	1	Unrelated
	Eye irritation	1	Possible
	Headache	2	Possible
	Headache	1	Possible
	Headache	1	Probable
	Hyperkalaemia	1	Unrelated
	Hyperkalaemia	1	Unrelated
	Leukopenia	1	Possible
	Musculoskeletal pain	1	Unrelated
	Musculoskeletal pain	2	Unrelated
	Nasopharyngitis	1	Unrelated
	Nasopharyngitis	2	Unrelated
	Neuropathy peripheral	1	Possible
	Pyrexia	3	Possible
	Rash	1	Possible
07/00003	Hypercholesterolaemia	2	Unrelated
	Hypertriglyceridaemia	1	Unrelated
	Hypocalcaemia	1	Unrelated
	Impaired healing	2	Probable
	Medical device removal	2	Unrelated
	Mucosal inflammation	1	Possible
07/00004	Anaemia	1	Unrelated
	Asthenia	2	Possible
	Constipation	2	Possible
	Decreased appetite	2	Possible
	Freezing phenomenon	1	Unrelated
	Headache	2	Possible
	Headache	2	Possible
	Hypercholesterolaemia	1	Unrelated
	Hypertriglyceridaemia	1	Unrelated
	Leukopenia	1	Unrelated
	Malaise	1	Unrelated
	Muscle spasms	1	Unrelated
	Neck pain	1	Possible
	Oedema peripheral	1	Possible
	Thrombocytopenia	1	Possible

9.2 Deaths, other serious and other significant adverse events

9.2.1 Deaths and severe adverse events

9.2.1.1 Severe adverse events (SAE)

A total of four SAEs were reported in four patients throughout the time of the study. The four reported SAEs were all of moderate Grade 3 toxicity. Two of the four documented SAEs (pyrexia and herpes zoster) were classified as possibly related to the intake of EVEROLIMUS (see 9.2.2.1). For the other two SAEs (epilepsy and hypersensitivity) a relationship with EVEROLIMUS maintenance was ruled out. All four SAEs resolved without sequelae.

Regarding the safety profile of EVEROLIMUS the two SAEs assessed as possibly study drug related are not unexpected adverse reactions. In fact pyrexia and infections are typical side effects of rapamycin derivatives due to their immunosuppressive properties.

0 presents an overview on documented SAEs sorted by CTC Grade. 0 provides a cumulative summary tabulation of all SAEs according to organ classes.

Table 14 Documented SAEs (CTC grade)

Description of SAE	Number of events	CTC grade 1	CTC grade 2	CTC grade 3	CTC grade 4
Epilepsy	1			1	
Herpes zoster	1			1	
Hypersensitivity	1			1	
Pyrexia	1			1	

Table 15 Cumulative tabulation of all SAEs by organ class

General disorders and administration site conditions	**1**
Pyrexia	1
Immune system disorders	**1**
Hypersensitivity	1
Infections and infestations	**1**
Herpes zoster	1
Nervous system disorders	**1**
Epilepsy	1

9.2.1.2 Specification of SAEs

Table 16 Specification of reported SAEs

PatientID	Description of SAE	Relation to study drug	Status of SAE
01/00001	Epilepsy	Unrelated	Resolved
01/00002	Herpes zoster	Possible	Resolved
07/00001	Hypersensitivity	Unrelated	Resolved
07/00002	Pyrexia	Possible	Resolved

01/00001 – Epilepsy
Patient 01/00001 experienced a generalized epileptic seizure on 03/01/2009 (day 17 on study treatment). The patient was admitted to a hospital as a case of emergency. The study drug was discontinued. An MRI scan of the brain was performed and revealed an old scar, probably due to a motorbike accident with traumatic brain injury in 1959. The administration of valproic acid was started as anticonvulsant.
Status of SAE: resolved
Relation to study drug: unrelated

01/00002 – Herpes zoster
Patient 01/00002 developed herpetiform lesions in the lumbal region on 11/02/2009 (day 6 on study drug). One day later study drug was discontinued and the patient had to be admitted to the dermatologic department for treatment of severe herpes zoster lumbalis (CTC grade 3). Aciclovir was administered intravenously from 11/12/2009-11/17/2009. While the skin lesions were resolving, the patient developed moderate leukopenia (CTC grade 3), possibly due to hematotoxic effects of the antiviral treatment. For this reason study medication could not be resumed until 12/29/2009.
Status of SAE: resolved
Relation to study drug: possible

07/00001 – Hypersensitivity

Patient 07/00001 suffered a hypersensitivity reaction while receiving a Rituximab infusion on 04/07/2009. Steroids were given and the patient was admitted to a local hospital. Symptoms improved and he could be discharged on 04/25/2009. For sake of completeness we report this SAE, although it occurred more than 30 days after the last intake of study drug, as the patient had discontinued EVEROLIMUS on 02/27/2009.
Status of SAE: resolved
Relation to study drug: unrelated

07/00002 – Pyrexia
Patient 07/00002 experienced fever of unknown origin on 01/05/2010 (day 452 on study treatment). The patient was admitted to a local hospital and treated with piperacillin and tazobactam empirically. The study medication was discontinued on 01/12/2010. Symptoms resolved and the patient could be discharged on 01/19/2010.
Status of SAE: resolved
Relation to study drug: possible

9.2.2 Other significant adverse events

9.2.2.1 Suspected Serious Adverse Reactions (SARs)

All in all two SARs had to be reported in the course of this study.

Table 17 Overview of SARs

General disorders and administration site conditions	**1**
Pyrexia	1
Infections and infestations	**1**
Herpes zoster	1

Suspected Unexpected Serious Adverse Reactions (SUSAR)

The sponsor's assessment of expectedness was determined by referring to the IB and SMPC. In the course of this clinical trial no SUSAR had to be reported.

However, SUSARs in relation EVEROLIMUS (RAD001, Afinitor®) being reported to Novartis Pharma AG by other institutions during the time of the study were provided to the MSZ by Novartis Pharma AG and the Ethics Committee and study centers were consecutively informed by the MSZ.

9.2.3 Evaluation of deaths and other serious or significant adverse events

Annual Safety Reports have been provided to the Health Authority and Ethics Committee for the following periods: January 2008 – December 2008, January 2009 – December 2009, January 2010 – December 2010. Besides, two Development Safety Reports were compiled for the periods of 12/28/10 - 12/27/11 and 12/28/11 - 12/27/12.

The reported AEs are consistent in quantity and quality with the known side effects profile of EVEROLIMUS. Taken together, a maintenance therapy with 5 mg EVEROLIMUS per day in patients suffering from MCL is safe according to its toxicity profile. Considering the maintenance setting, however patients' tolerability of these side effects was poor being reflected in the premature discontinuation of study medication in 5/8 patients on personal request.

During study conduct various changes in SMPC and IB have been made, which were promptly communicated to the study centres and the EC along with new and relevant findings related to safety. In order to reflect these changes the Patient Informed Consent had to be changed once. However, the risk-benefit evaluation for the clinical trial deemed not to be affected. While generally confirmed by the safety evaluation of the ISMB, the present safety assessment would have been estimated as critically compromised in case of occurrence of another epileptic seizure.

9.3 Laboratory values

A specific panel of laboratory analyses had to be assessed at predefined time points throughout the study conduct. (Please refer to chapter 4.5.1 of the study protocol). Relevant findings in the measured laboratory parameters were documented as AEs in the CRF (see 0, 0 and 0).

9.4 Vital signs

Vital signs were captured starting at baseline and during following visits. Values were not deemed to prevent entry of the patient into the study. Significant observations in vital signs were documented as AEs in the CRF (see 0, 0 and 0).

9.5 Special safety topics

There are no additional topics for discussion.

10 Discussion and overall conclusions

10.1 Discussion

Treatment of MCL which is characterized by the t(11;14)(q13; q32) chromosomal translocation leading to constitutive cyclin D1 overexpression is still challenging, as this subtype of B cell Non-Hodgkin lymphoma (B-NHL) usually shows an aggressive clinical course with a continuous relapse pattern and a median survival of three to seven years [Herrmann, 2009].

In untreated MCL patients standard chemoimmunotherapy regimens, e. g. R-CHOP or R-Bendamustin, provide high overall remission rates. These responses however are usually not durable necessitating sequential therapies in the course of the disease [Howard, 2002; Rummel, 2013]. Younger patients having received at least a partial remission after conventional chemoimmunotherapy should therefore be offered consolidation with high-dose therapy followed by autologous SCT to consolidate response and prolong remission [Dreyling 2005; Geisler, 2012; LaCasce, 2012]. Since MCL is predominantly a disease of the elderly [Smedby, 2011], a significant proportion of patients is not eligible for such intensive treatment options. Thus, strategies to prolong the response duration leading to an improvement of the poor prognosis for those patients are urgently needed.

The concept of a maintenance treatment after induction chemoimmunotherapy emerged as interesting approach in this context. Several years ago maintenance therapy with IFN-α was shown to trend to a prolongation of progression-free survival in MCL patients [Hiddemann, 1996]. A few years later a maintenance regimen with the Anti-CD20 mAb Rituximab was shown to significantly improve the duration of response in patients with relapsed FL or MCL [Forstpointner 2006].

As it is known that constitutive activation of the PI3K/Akt signaling pathway contributes to the pathogenesis of MCL [Rudelius 2006], inhibition of this pathway, e. g. by using an mTOR inhibitor, emerged as attractive therapeutic target for this B-NHL subtype. Due to convincing results regarding overall response rate and progression-free survival in several clinical trials, including one prospective, randomized Phase III trial, the mTOR inhibitor Temsirolimus has been approved for the treatment relapsed or refractory MCL in Europe [Witzig 2005b; Ansell 2008; Hess 2009].

EVEROLIMUS (RAD001; 40-O-[-2-hydroxyethyl]-Rapamycin) is another potent and orally bioavailable inhibitor of the mTOR pathway, which has been shown to effectively inhibit proliferation and growth of several cancer cell lines *in vitro* and a range of tumor types in experimental animal models [Lane, 2006]. Several clinical trials have shown preliminary efficacy of EVEROLIMUS as single agent in patients suffering from a broad range of aggressive subtypes of relapsed B-NHL, including MCL [Tobinai 2010; Witzig 2011; Renner 2012].

As described above, our study intended to assess efficacy and feasibility of a maintenance therapy with EVEROLIMUS in patients with MCL having received disease control after first, second, third or fourth line chemotherapy (under protocol V.2.0 only first and second line patients were included) and who were not eligible for intensive chemotherapy regimens. Primary endpoint for assessing efficacy of this maintenance regimen in the study was time to progression. As secondary endpoints safety and feasibility (overall survival, quality of life, duration of responses) were assessed.

Altogether only 8/25 patients were included into the study. Due to slower than expected recruitment, the study was prematurely closed in 2012.

None of the eight patients enrolled into the study completed the initially intended period for maintenance therapy of 24 months. All eight patients prematurely ended the study, five patients on personal request, two patients had to finish maintenance therapy due to disease progression. One patient had to stop maintenance with EVEROLIMUS due to drug interactions with valproic acid he was put on as anticonvulsant after an epileptic seizure.

All in all five patients relapsed within 24 months after study inclusion. One patient was lost to follow up 17.4 months after study inclusion without documented disease progression. Two patients did not suffer disease progression within 24 months after study inclusion. For the five patients with documented disease progression, time to progression ranged from 4.8 to 25.6 months.

One patient died 9.7 months after study inclusion. The documented reason for death in this case was disease progression.

A total of 85 AEs and four SAEs were documented in the eight patients included into the study. Most AEs were classified as grade 1 or 2 toxicity (76 AEs of CTC-grade 1/2; 9 AEs of CTC-grade 3; no AE of CTC-grade 4). The four SAEs were observed in four different patients. Two SAEs were not related to the study drug and two SAEs were possibly related to intake of EVEROLIMUS (SARs). The SARs, classified as possibly related to the study drug, resolved both without sequelae. No SUSAR was documented.

Based on the results of the limited patient population of this clinical study, maintenance therapy with EVEROLIMUS can be considered as safe in patients with MCL having received disease control after one or two lines of chemotherapy and not being eligible for intensive chemotherapy regimens. However, no patient concluded the planned period of 24 months of maintenance therapy; most patients stopped therapy prematurely upon their own request.

Being aware of the results from the European MCL Elderly trial, in the meantime a new standard treatment for elderly patients with MCL (bimonthly Rituximab maintenance until relapse after R-CHOP induction) has been established [Kluin-Nelemans 2012].

However, since it has become evident that mTOR inhibitors trigger pleiotrophic effects besides the downregulation of cyclin D1 contributing to their cyctotoxic effects, combination of rapamycin derivatives with established regimes seems to be an attractive option to establish potential synergistic effects. For example in the currently recruiting phase I/II BERT trial temsirolimus has been successfully combined with Rituximab and bendamustin for treatment of patients with relapsed MCL or FL [Hess, 2011].

10.2 Conclusions

Due to the small number of eight patients included in this clinical trial, our study can only be considered as a pilot investigation without the power to draw statistical conclusions.

Since frequency and severity of the observed AEs were in the expected range, it can be concluded that a maintenance therapy with EVEROLIMUS is safe in patients with MCL having received disease control after one or two lines of chemotherapy and not being eligible for intensive chemotherapy regimens. Regarding feasibility we observed in our small patient population a high proportion of patients prematurely discontinuing study medication on personal request. So obviously the occurring AEs together with the subjective perceived

deterioration of general health status and quality of life during continuous medication with EVEROLIMUS were unacceptable for many patients, especially as they were in a maintenance setting, knowing their disease controlled.

So, all in all we come to the conclusion that EVEROLIMUS is not a satisfactory option for a continuous maintenance concept in our patient collective, but as EVEROLIMUS can be safely applied, there is potential for combination with chemotherapy regimens in the future.

11 Reference list

ADDIN EN.REFLIST Ansell, S. M., D. J. Inwards, K. M. Rowland, Jr., P. J. Flynn, R. F. Morton, D. F. Moore, Jr., S. H. Kaufmann, I. Ghobrial, P. J. Kurtin, M. Maurer, C. Allmer and T. E. Witzig (2008). "Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group." Cancer **113**(3): 508-14.

Bjornsti, M. A. and P. J. Houghton (2004). "The TOR pathway: a target for cancer therapy." Nat Rev Cancer **4**(5): 335-48.

Cheson, B. D., S. J. Horning, B. Coiffier, M. A. Shipp, R. I. Fisher, J. M. Connors, T. A. Lister, J. Vose, A. Grillo-Lopez, A. Hagenbeek, F. Cabanillas, D. Klippensten, W. Hiddemann, R. Castellino, N. L. Harris, J. O. Armitage, W. Carter, R. Hoppe and G. P. Canellos (1999). "Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group." J Clin Oncol **17**(4): 1244.

Dreyling, M., G. Lenz, E. Hoster, A. Van Hoof, C. Gisselbrecht, R. Schmits, B. Metzner, L. Truemper, M. Reiser, H. Steinhauer, J. M. Boiron, M. A. Boogaerts, A. Aldaoud, V. Silingardi, H. C. Kluin-Nelemans, J. Hasford, R. Parwaresch, M. Unterhalt and W. Hiddemann (2005). "Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network." Blood **105**(7): 2677-84.

Fernandez, V., E. Hartmann, G. Ott, E. Campo and A. Rosenwald (2005). "Pathogenesis of mantle-cell lymphoma: all oncogenic roads lead to dysregulation of cell cycle and DNA damage response pathways." J Clin Oncol **23**(26): 6364-9.

Forstpointner, R., M. Unterhalt, M. Dreyling, H. P. Bock, R. Repp, H. Wandt, C. Pott, J. F. Seymour, B. Metzner, A. Hanel, T. Lehmann, F. Hartmann, H. Einsele and W. Hiddemann (2006). "Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG)." Blood **108**(13): 4003-8.

Geisler, C. H., A. Kolstad, A. Laurell, M. Jerkeman, R. Raty, N. S. Andersen, L. B. Pedersen, M. Eriksson, M. Nordstrom, E. Kimby, H. Bentzen, O. Kuittinen, G. F. Lauritzsen, H. Nilsson-Ehle, E. Ralfkiaer, M. Ehinger, C. Sundstrom, J. Delabie, M. L. Karjalainen-Lindsberg, P. Brown and E. Elonen (2012). "Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur." Br J Haematol **158**(3): 355-62.

Gianni, A. M., M. Magni, M. Martelli, M. Di Nicola, C. Carlo-Stella, S. Pilotti, A. Rambaldi, S. Cortelazzo, C. Patti, G. Parvis, F. Benedetti, S. Capria, P. Corradini, C. Tarella and T. Barbui (2003). "Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen)." Blood **102**(2): 749-55.

Hay, N. and N. Sonenberg (2004). "Upstream and downstream of mTOR." Genes Dev **18**(16): 1926-45.

Herrmann, A., E. Hoster, T. Zwingers, G. Brittinger, M. Engelhard, P. Meusers, M. Reiser, R. Forstpointner, B. Metzner, N. Peter, B. Wormann, L. Trumper, M. Pfreundschuh, H. Einsele, W. Hiddemann, M. Unterhalt and M. Dreyling (2009). "Improvement of overall survival in advanced stage mantle cell lymphoma." J Clin Oncol **27**(4): 511-8.

Hess, G., R. Herbrecht, J. Romaguera, G. Verhoef, M. Crump, C. Gisselbrecht, A. Laurell, F. Offner, A. Strahs, A. Berkenblit, O. Hanushevsky, J. Clancy, B. Hewes, L. Moore and B. Coiffier (2009). "Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma." J Clin Oncol **27**(23): 3822-9.

Hess, G. K., U. Atta J. Buske C. Borchmann P. Medler C. Witzens-Harig M. Dreyling M. (2011). "Temsirolimus in combination with bendamustin and rituximab for the treatment of relapsed mantle cell and follicular lymphoma: report on an ongoing phase I/II trial." Blood **118**(suppl 1): #2697.

Hiddemann, W., F. Griesinger and M. Unterhalt (1998). "Interferon alfa for the treatment of follicular lymphomas." Cancer J Sci Am **4 Suppl 2**: S13-8.

Hiddemann, W., M. Unterhalt and B. Wormann (1996). "[Therapy of low-grade non-Hodgkin lymphomas]." Praxis (Bern 1994) **85**(12): 357-63.

Howard, O. M., J. G. Gribben, D. S. Neuberg, M. Grossbard, C. Poor, M. J. Janicek and M. A. Shipp (2002). "Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival." J Clin Oncol **20**(5): 1288-94.

Kluin-Nelemans, H. C., E. Hoster, O. Hermine, J. Walewski, M. Trneny, C. H. Geisler, S. Stilgenbauer, C. Thieblemont, U. Vehling-Kaiser, J. K. Doorduijn, B. Coiffier, R. Forstpointner, H. Tilly, L. Kanz, P. Feugier, M. Szymczyk, M. Hallek, S. Kremers, G. Lepeu, L. Sanhes, J. M. Zijlstra, R. Bouabdallah, P. J. Lugtenburg, M. Macro, M. Pfreundschuh, V. Prochazka, F. Di Raimondo, V. Ribrag, M. Uppenkamp, M. Andre, W. Klapper, W. Hiddemann, M. Unterhalt and M. H. Dreyling (2012). "Treatment of older patients with mantle-cell lymphoma." N Engl J Med **367**(6): 520-31.

Krymskaya, V. P. (2003). "Tumour suppressors hamartin and tuberin: intracellular signalling." Cell Signal **15**(8): 729-39.

LaCasce, A. S., J. L. Vandergrift, M. A. Rodriguez, G. A. Abel, A. L. Crosby, M. S. Czuczman, A. P. Nademanee, D. W. Blayney, L. I. Gordon, M. Millenson, A. Vanderplas, E. M. Lepisto, A. D. Zelenetz, J. Niland and J. W. Friedberg (2012). "Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database." Blood **119**(9): 2093-9.

Lane, H. A. and D. Lebwohl (2006). "Future directions in the treatment of hormone-sensitive advanced breast cancer: the RAD001 (Everolimus)-letrozole clinical program." Semin Oncol **33**(2 Suppl 7): S18-25.

Lefrere, F., A. Delmer, V. Levy, R. Delarue, B. Varet and O. Hermine (2004). "Sequential chemotherapy regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma: an update of a prospective study." Haematologica **89**(10): 1275-6.

Lenz, G., M. Dreyling, E. Schiegnitz, R. Forstpointner, H. Wandt, M. Freund, G. Hess, L. Truemper, V. Diehl, M. Kropff, M. Kneba, N. Schmitz, B. Metzner, M. Pfirrmann, M. Unterhalt and W. Hiddemann (2004). "Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free

survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group." Blood **104**(9): 2667-74.

Li, Z. M., E. Zucca and M. Ghielmini (2013). "Open questions in the management of mantle cell lymphoma." Cancer Treat Rev **39**(6): 602-9.

Majumder, P. K., P. G. Febbo, R. Bikoff, R. Berger, Q. Xue, L. M. McMahon, J. Manola, J. Brugarolas, T. J. McDonnell, T. R. Golub, M. Loda, H. A. Lane and W. R. Sellers (2004). "mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways." Nat Med **10**(6): 594-601.

Mangel, J., H. A. Leitch, J. M. Connors, R. Buckstein, K. Imrie, D. Spaner, M. Crump, N. Pennell, A. Boudreau and N. L. Berinstein (2004). "Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis." Ann Oncol **15**(2): 283-90.

Panwalkar, A., S. Verstovsek and F. J. Giles (2004). "Mammalian target of rapamycin inhibition as therapy for hematologic malignancies." Cancer **100**(4): 657-66.

Renner, C., P. L. Zinzani, R. Gressin, D. Klingbiel, P. Y. Dietrich, F. Hitz, M. Bargetzi, W. Mingrone, G. Martinelli, A. Trojan, K. Bouabdallah, A. Lohri, E. Gyan, C. Biaggi, S. Cogliatti, F. Bertoni, M. Ghielmini, P. Brauchli and N. Ketterer (2012). "A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma." Haematologica **97**(7): 1085-91.

Romaguera, J. E., L. Fayad, M. A. Rodriguez, K. R. Broglio, F. B. Hagemeister, B. Pro, P. McLaughlin, A. Younes, F. Samaniego, A. Goy, A. H. Sarris, N. H. Dang, M. Wang, V. Beasley, L. J. Medeiros, R. L. Katz, H. Gagneja, B. I. Samuels, T. L. Smith and F. F. Cabanillas (2005). "High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine." J Clin Oncol **23**(28): 7013-23.

Rudelius, M., S. Pittaluga, S. Nishizuka, T. H. Pham, F. Fend, E. S. Jaffe, L. Quintanilla-Martinez and M. Raffeld (2006). "Constitutive activation of Akt contributes to the pathogenesis and survival of mantle cell lymphoma." Blood **108**(5): 1668-76.

Rummel, M. J., N. Niederle, G. Maschmeyer, G. A. Banat, U. von Grunhagen, C. Losem, D. Kofahl-Krause, G. Heil, M. Welslau, C. Balser, U. Kaiser, E. Weidmann, H. Durk, H. Ballo, M. Stauch, F. Roller, J. Barth, D. Hoelzer, A. Hinke and W. Brugger (2013). "Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial." Lancet **381**(9873): 1203-10.

Shayesteh, L., Y. Lu, W. L. Kuo, R. Baldocchi, T. Godfrey, C. Collins, D. Pinkel, B. Powell, G. B. Mills and J. W. Gray (1999). "PIK3CA is implicated as an oncogene in ovarian cancer." Nat Genet **21**(1): 99-102.

Smedby, K. E. and H. Hjalgrim (2011). "Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes." Semin Cancer Biol **21**(5): 293-8.

Tobinai, K., M. Ogura, D. Maruyama, T. Uchida, N. Uike, I. Choi, K. Ishizawa, K. Itoh, K. Ando, M. Taniwaki, N. Shimada and K. Kobayashi (2010). "Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma." Int J Hematol **92**(4): 563-70.

Weisenburger, D. D., W. G. Sanger, J. O. Armitage and D. T. Purtilo (1987). "Intermediate lymphocytic lymphoma: immunophenotypic and cytogenetic findings." Blood **69**(6): 1617-21.

Witzens-Harig, M., G. Hess, J. Atta, M. Zaiss, G. Lenz, C. Scholz, R. Repp, M. Reiser, C. Pott, H. Pelz, P. La Rosee, H. Kirchner, P. Kiewe, U. Keller, C. Buske, A. Viardot and M. Dreyling (2012). "Current treatment of mantle cell lymphoma: results of a national survey and consensus meeting." Ann Hematol **91**(11): 1765-72.

Witzig, T. E. (2005a). "Current treatment approaches for mantle-cell lymphoma." J Clin Oncol **23**(26): 6409-14.

Witzig, T. E., S. M. Geyer, I. Ghobrial, D. J. Inwards, R. Fonseca, P. Kurtin, S. M. Ansell, R. Luyun, P. J. Flynn, R. F. Morton, S. R. Dakhil, H. Gross and S. H. Kaufmann (2005b). "Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma." J Clin Oncol **23**(23): 5347-56.

Witzig, T. E., C. B. Reeder, B. R. LaPlant, M. Gupta, P. B. Johnston, I. N. Micallef, L. F. Porrata, S. M. Ansell, J. P. Colgan, E. D. Jacobsen, I. M. Ghobrial and T. M. Habermann (2011). "A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma." Leukemia **25**(2): 341-7.