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

Authors:	Prof. Dr. Ulrich Keller, Dr. Susanne Schreiber
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Study Report Synopsis

Sponsor: Technische Universität München (TUM), Fakultät für Medizin, Ismaninger Straße 22, 81675 München
Name of Finished Product: Afinitor®
Name of Active Ingredient: EVEROLIMUS (RAD001)
Study Title: 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 Number: 2007-005116-12
Coordinating Investigator (Sponsor Delegated Person): 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 (no patients included) 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 patients included) 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 patients included) Hämatologie / Onkologie Principal Investigator: Prof. Stephan Stilgenbauer Klinik für Innere Medizin III Albert-Einstein-Allee 23 89081 Ulm

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Tel.: 0731 500 457 13; Fax: 0731 500 244 05 E-Mail: stephan.stilgenbauer@uniklinik-ulm.de **5.** not applicable **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 (no patients included) 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 (no patients included) 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	
Publication (reference): not published yet	
Studied period (years) **First patient included:** 19.09.2008 **Last patient completed:** 22.02.2011 **Premature Termination:** The clinical study was terminated prematurely in 2012 due to slower than anticipated recruitment. **Protocol amendments**: Amendment 1: On 20.03.2008 protocol version 2.0 (changes from Version 1.0. to 2.0 due to EC request) was approved by the EC. All	Non-randomized, open-label, multicentre, Phase II trial

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eight patients included into the clinical trial were included under this protocol version.

Amendment 2: Protocol V.3.0 (allowing enrollment not only of first and second line patients, but also of third and fourth line patients) dating from 01.09.2010 was approved by the EC on 25.10.2010. No patients were included according to the new inclusion criteria (Last patient included: 19.10.09).

Changes to the informed consent form to reflect new safety information of EVEROLIMUS were approved by the EC on 21.04.2011.

Amendment 3: Protocol V.4.0 (new data, patient number reduced from 35 to 25, reviewed endpoints (after new data on the study drug, PK assessments were redundant), descriptive statistics, reviewed table of events (clarification of end of treatment/end of study after follow-up) dating from 01.08.2011 was approved by the EC on 07.09.2011.

Analysis of the patient population to be performed according to the current protocol version 4.0., since this version consists in an amelioration and precision of the older versions.

Study Design:
An investigator-initiated non-randomized, prospective, open-label, multicenter, interventional Phase II clinical 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 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

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- To analyze Quality of life during maintenance therapy

Number of patients (planned and analyzed):

Planned sample size: 25 patients

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

Patient Population:

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

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)

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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:
EVEROLIMUS in MCL patients, administered orally as single daily dose of 5 mg (5 mg and 2.5 mg tablets).

Batch numbers (Ch.-B):
9758 and 9928 (distributed by the pharmacy of TUM, 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.

In none of the patients study medication could be administered for 24 months. Premature discontinuation of EVEROLIMUS maintenance was necessary due to progression of disease in 2/8 patients and adverse events (AE) or on patients' request in 6/8 patients.

Reference therapy, Comparator: No, not applicable

Blinding:
No

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).

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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 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%.

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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. Coding: MedDRA-Version 14.1 English

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) 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.

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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: 19.09.2008; last patient included: 19.10.2009). 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 regimens, for MCL treatment before. All patients had been exposed to Rituximab.

Compliance

Protocol Deviations (PD):

Seven PD were reported in 6/8 patients: Two patients violated inclusion criteria (one patient platelets were not ≥ 100 x 10^9/L, and one patient had not achieved disease control after one to two lines of chemotherapy); one patient continued treatment after 21 days of interruption even though treatment should have been discontinued; the other PD were rated as minor (i.e. change in timing).

Study medication:

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.

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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):

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

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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, 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.

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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.

AEs were graded according to the NIH/NCI CTCAEv3.pdf. AE/SAE were coded according to MedDRA V. 14.1 English.

Independent Safety Monitoring Board

The ISMB independently reviewed the safety data during study duration. 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. (Table 1: Cumulative summary of AE sorted by organ class)

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. 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. (Table 2: Cumulative summary of SAE sorted by organ class)

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Suspected Serious Adverse Reactions (SARs):
A total of two SARs were reported in the course of this study (pyrexia and herpes zoster). (Table 3: Cumulative summary of SAR sorted by organ class)

Suspected Unexpected Serious Adverse Reactions (SUSAR)
The sponsor's assessment of expectedness was determined by referring to the IBs and 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: amended version 2.0 01.10.2020

Table 1 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 22 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

Table 3 Overview of SARs

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