SYNOPSIS ANNEX I

A phase I/II trial to evaluate the safety, feasibility and efficacy of the addition of Temsirolimus (Torisel™) to a regimen of Bendamustine and Rituximab for the treatment of patients with follicular lymphoma or mantle cell lymphoma in first to third relapse

EudraCT-No.: 2009-013351-30

Vorlage-Nr.: 4035783

1) **Name of Sponsor/Company:**

University Medical Center of the Johannes Gutenberg-University Mainz

Represented by the executive board of the University
Represented by the scientific member of the executive board
Univ.-Prof. Dr. U. Förstermann

Delegated to operating institution:
Department of Hematology, Oncology and Pneumology
University Medical Center of the Johannes Gutenberg-University
Langenbeckstr. 1, 55131 Mainz, Germany
Director: Univ.-Prof. Dr. M. Theobald
Delegated to the CI Univ.-Prof. Dr. G. Hess

2) **Name of Finished Product:**

Ribomustin/Levact

MabThera

Torisel

3) **Name of Active Substance:**

Bendamustine

Rituximab

Temsirolimus

4) **Individual Study Table Referring to Part of the Dossier:** na

Volume: na

Page: na

5) **Title of Study:**
A phase I/II trial to evaluate the safety, feasibility and efficacy of the addition of Temsirolimus (Torisel™) to a regimen of Bendamustine and Rituximab for the treatment of patients with follicular lymphoma or mantle cell lymphoma in first to third relapse

Substantial amendment 1, protocol 2.0 (22.11.2010)

Substantial amendment 2, protocol 2.1 (16.08.2012)

6) **Principal Investigator(s):**

Coordinating Investigator: Univ.-Prof. Dr. med. Georg Heß

7) **Study centre(s):**

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SYNOPSIS **ANNEX I**

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EudraCT-No.: 2009-013351-30

Vorlage-Nr.: 4035783

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8) **Publication (reference):**

Hess G, Keller U, Scholz CW, Witzens-Harig M, Atta J, Buske C, Kirschey S, Ruckes C, Medler C, van Oordt C, Klapper W, Theobald M, Dreyling M. Safety and efficacy of temsirolimus in combination with bendamustine and rituximab in relapsed mantle cell and follicular lymphoma. Leukemia 2015; 29: 1695-701.

9) **Studied period (years):**	10) **Phase of development:** I/II
Date of first enrolment: 02-FEB-2010	
Date of last completed: 05-APR-2017	

11) **Objectives:**

Phase I:

Primary: To establish a maximum tolerated dose of the addition of Temsirolimus to a regimen of Bendamustine and Rituximab (BERT) in patients with relapsed follicular lymphoma and mantle cell lymphoma.

Phase II:

Primary: To evaluate the ORR in patients with MCL or FL treated with the established BERTdose.

Secondary: To determine the complete remission rate, progression free survival rate and overall survival rate and to investigate safety and tolerability of BERT.

12) **Methodology:**

This is a multicenter, open label, single arm, phase I/II study. There will be no placebo usage within this trial.

The first part of the study is a phase I study in which the maximum tolerated dose of the combination of Temsirolimus, Bendamustine and Rituximab will be established. In the phase I part of the trial 3 patients will be included in each dose level. After inclusion of 3 patients, each patient has to receive at least 2 complete cycles without DLT until the enrolment into the next cohort can be initiated. In case of one DLT, 3 additional patients will be added to the specific dose level. If a second DLT appears, the last dose level without DLT will be considered the standard dose for the phase II trial. If the third dose level is achieved without any DLT, there will be no further dose escalation.

In the phase II proportion of the trial, after establishment of a maximum tolerated dose, the efficacy of the combination regimens in two different patient cohorts will be evaluated. In the one cohort, 30 patients with relapsed mantle cell lymphoma will be treated; the second cohort will be composed of 30 patients with relapsed follicular lymphoma.

13) **Number of patients (planned and analyzed):**

Phase I: 6-18 (planned); 15 (analyzed)

Phase II: 60 (30 each stratum, planned); 24 (analyzed)

14) **Diagnosis and main criteria for inclusion:**

Confirmed mantle cell lymphoma (including cyclin D1 expression) or follicular lymphoma (grades I-IIIA) in 1st, 2nd or 3rd relapse, aged >/= 18 years, no transplantation option available, given informed consent, adequate hepatic and renal function, adequate bone marrow reserve (PLT > 75.000/µl, ANC > 1500/µl), no severe concomitant disease, pregnancy or breast feeding, intolerance to one of the study drugs , ECOG 0-2.

15) **Test product, dose and mode of administration, batch number:**

Dosage and administration: BERT: Dose Escalation phase I

Phase I – Cohort A

Bendamustine 90mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 25mg, day 2, 8, 15, repeat day 30

Phase I – Cohort B

Bendamustine 90mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 50mg, day 2, 8, 15, repeat day 30

Phase I – Cohort C

Bendamustine 90mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 75mg, day 2, 8, 15, repeat day 30

In case of DLT in Cohort A (with respect to recommendation of safety review committee, dose level A-2 or A-1 will be used for restart of the trial)

Phase I – Cohort A-1

Bendamustine 60mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 25mg, day 2, 8, 15, repeat day 30

Phase I – Cohort A-2

Bendamustine 60mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 15mg, day 2, 8, 15, repeat day 30

Dosage and administration: BERT: phase II

After evaluation of phase I dosage for phase II has been selected as follows.

BERT: Maximum target dose in phase II, 4 cycles

Bendamustine 90mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 50mg, day 2, 8, 15, repeat day 30

Batch Numbers:

H0514B01 02.14;H0514B01 02.14; H0514B01 02.14; H0514B01 02.14; 99409 08/14;99409 08/14; 99278 03/14;99278 03/14; 99278 03/14;99409 08/14; AFSD/1H 06/12; AFSD/1H 06/12; AFSD/1H 06/12; AFSD/1H 06/12; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; 99409 08/14; 99728 03/14; 99728 03/14; 99728 03/14; H0521B01 02.14; H0521B01 02.14; 99409 08/14; 99728 03/14; 99728 03/14; 99728 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; 100031 03/14; 99278 03/14; 99278 03/14; 99278 03/14

H0535 B01 05.14; H0535 B01 05.14; 100031 03/14; 99278 03/14; 99278 03/14; 99278 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14; AGBV/99 03/14

16) **Duration of treatment:** Maximum of 4 treatment cycles. One treatment cycle lasts 4 weeks.

17) **Reference therapy, dose and mode of administration, batch number:** Not applicable.

18) **Criteria for evaluation:**

Efficacy:

The primary objective of the phase I part of the trial was:

The determination of a maximum tolerated dose (MTD) of the addition of Temsirolimus to a combination of Bendamustine and Rituximab (BERT)

The primary objective of the phase II part of the trial was:

The determination of the objective response rate (number of patients with PR and CR) in patients with relapsed mantle cell or follicular lymphoma treated at the maximum tolerated dose of BERT.

The secondary objectives for both study arms were as follows:

Overall response rate (phase I), as defined as the sum of the patients achieving a complete or partial remission (CR, PR)

Duration of response; as defined as the period from the first response (at least PR) to treatment until evidence of disease progression

Progression free survival, as defined as the time from the initiation of treatment until the first evidence of disease progression or death, whatever comes first

Overall survival, as defined as the time from the initiation of treatment until death

Safety and tolerability of BERT, as defined as the percentage of patients experiencing grade III - V toxicities according to CTC-criteria

Time to subsequent lymphoma therapy, as defined as the time from the initiation of treatment until the initiation of the first subsequent treatment

Treatment free interval, as defined as the time from the end of study treatment until the initiation of the subsequent treatment

Safety:

Frequency of adverse events will be calculated. Adverse events will be classified by system organ class and preferred term according to MedDRA terminology. Further analyses of adverse events comprise duration, whether the AE was serious, intensity, relationship to trial treatment, action taken and clinical outcome.

19) **Statistical methods:**

Calculation of remission and response rates is done by standard descriptive statistics. 95% confidence intervals are provided to reflect the extent of uncertainty.

Calculation of median progression free survival, overall survival etc. is performed by the method established by Kaplan and Meier.

Frequency of adverse events will be calculated. Adverse events will be classified by system organ class and preferred term according to MedDRA terminology. Further analyses of adverse events comprise duration, whether the AE was serious, intensity, relationship to trial treatment, action taken and clinical outcome.

20) **Summary – Conclusions:**

Background: mTOR inhibition has been shown to be effective in various subtypes of malignant lymphomas (Smith et al, JCO 2010). Furthermore, in relapsed MCL a phase III trial could prove superiority of Temsirolimus to chemotherapy. Subsequently, several trials could show, that combination to other agents like Rituximab (Ansell et al, Lancet Oncology 2011) or chemoimmunotherapy gives promising results, as recently reported (Hess, Leukemia, 2015). In the later trial promising results were observed in phase I and we provide the final analysis of phase I and II results.

Overall 39 patients (pts) were included (15 pts phase I, 24 pts phase II): 29 MCL and 10 FL, median age was 71 years, 28 were male (72%) and 11 were female (28%). All patients were Caucasian. 13 pts (35%) had an ECOG status of 1 and 24 (65%) had an ECOG status of 0.

Lymphoma staging showed 1 pt (3%) Stage 1, 5 pts (13%) Stage 2, 6 pts (15%) Stage 3, and 27 pts (69%) Stage 4. Tumor size was 5.5cm ± 3.0 on average, whereas 20 pts (53%) had a tumor size of > 5.0 cm and 8 pts (21%) had even a tumor size of >7.5 cm. In 13 pts (35%) an involvement of the bone marrow was documented.

The median number of pretreatments was 2 (1-3). The most recent response to the most recent therapy was CRu 7 pts (19%), PRu 6 pts (16%), SDu 7 pts (19%), PDu 15 pts (41%), 4 pts had an unknown or missing most recent response assessment. 2 pts had received prior radio therapy, 2 pts had received a prior stem cell transplantation and further 2 pts had received both.

All evaluated patients started at least one treatment cycle with a median number of 4 started treatment cycles. The mean duration of the follow up was 897 ± 499 days. The compliance to study medications was very high: Bendamustine: 99.6%, Rituximab: 100.0%, Temsirolimus: 96.8% on average.

Efficacy results:

MTD: In the phase I part of this trial, 50 mg of Temsirolimus (days 2, 8, 15) combined with 90 mg/m² BSA Bendamustin (day 1) and 375 mg/m² BSA Rituximab (day 1) was established as maximum tolerated dose subsequently used in the phase II part of this trial.

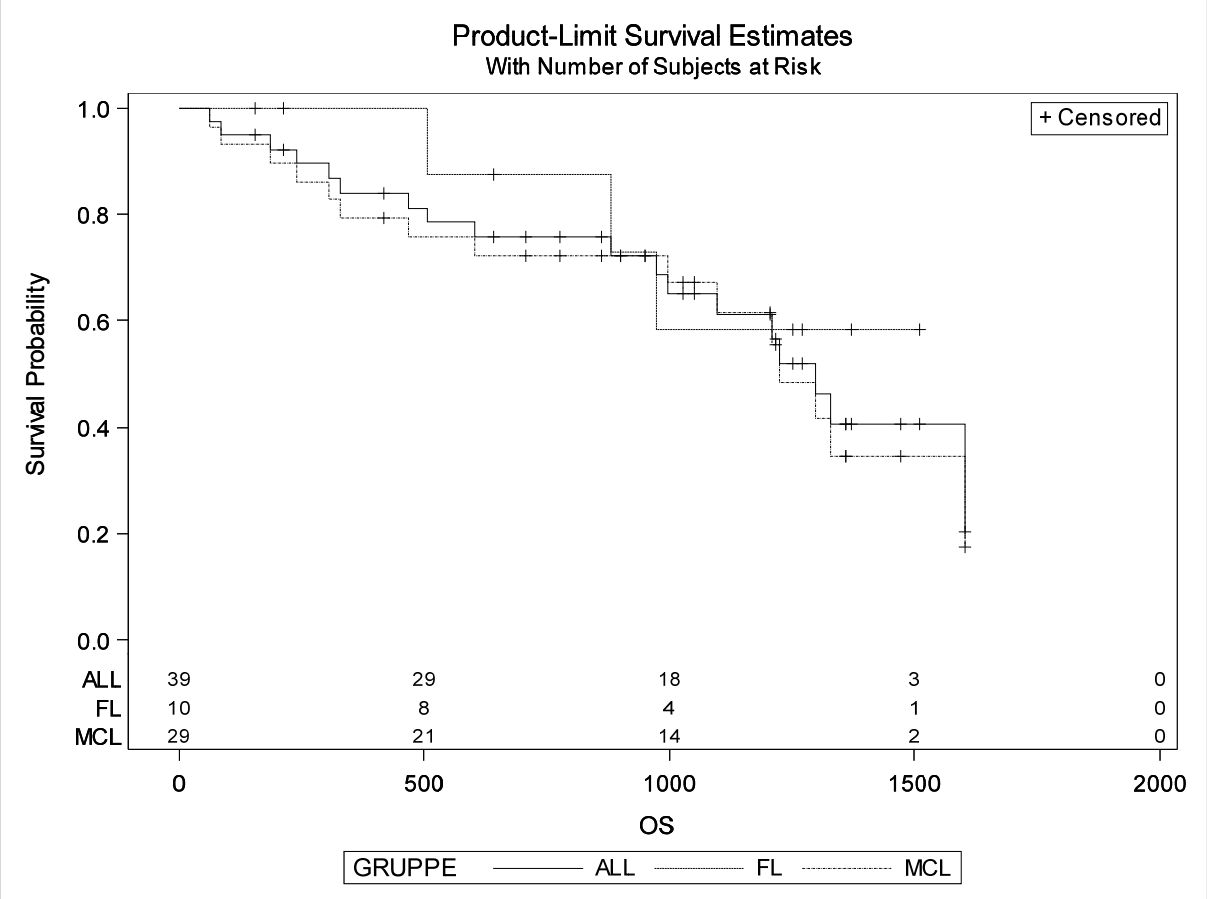
Response:

Overall responses after the treatment phase were 3 CR (9%), 23 PR (70%), 4 SD (12%) and 3 PD (9%), 11 pts were not assessable at this time point~~)~~ resulting in an ORR of 67% (=26/39). At the end of the individual follow-up the overall responses of (8 CR (28%), 6 PR (21%), 0 SD (0%) and 15 PD (52%), 10 pts were not assessable at the follow-up) were observed resulting in an ORR of 36% (=14/39).

The best responses considering treatment phase and follow-up were 14 CR (38%), 19 PR (51%) and 4 SD (11%). For 2 patients no valid response assessment was done. The best responses referring to the treatment phase only were 4 CR (11%), 27 PR (75%) and 5 SD (14%). For 3 patients no response assessment could be assessed.

The Kaplan-Meier curve for the overall survival is displayed in the following graph 1.

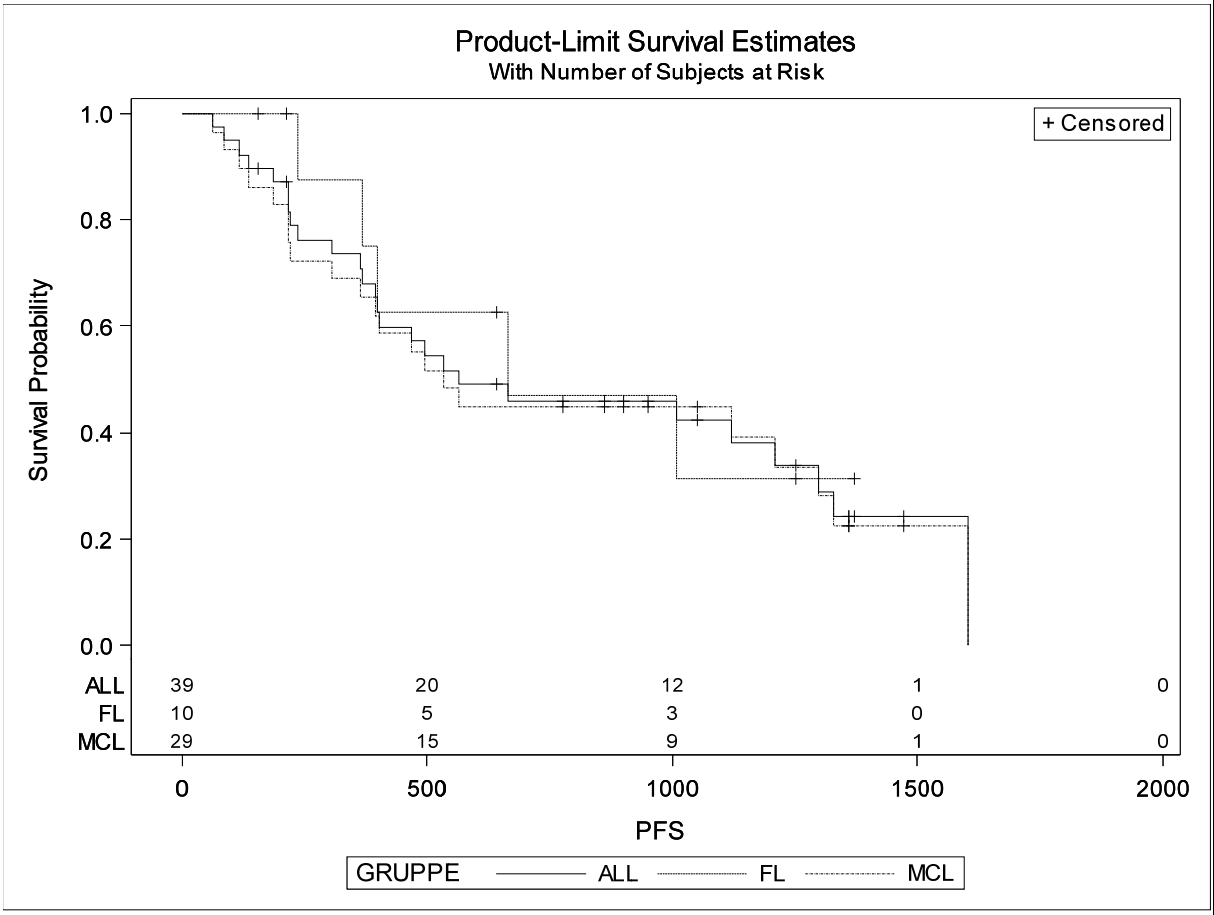
Graphic 1: Overall survival – Kaplan-Meier estimates



The median overall survival was 3.6 years with a 95% confidence interval of (2.7,∞).

The following graph shows the Kaplan-Meier plot of the progression free survival.

Graphic 2: Progression-free survival – Kaplan-Meier estimates



The median progression-free survival was 1.5 years with a 95% confidence interval of (1.1,3.6).

Safety results:

Definitions of adverse events (AE), serious adverse events (SAE), adverse reactions and suspected unexpected serious adverse reactions (SUSAR) are given in the trial protocol. All AEs reported by the subject or detected by the investigator were documented on the appropriate pages of the electronic case report form (eCRF). The sponsor of the clinical trial ensured that all legal reporting requirements were met. All AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA).

Amendment 2.1 of the study protocol excluded lymphopenia from definition of reportable AEs, as it is an expected event as result of rituximab treatment. Thus, lymphopenia was only documented for the first part of the enrolled patients and so frequency of lymphopenia cannot be compared to frequency of other AE terms.

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All 39 patients enrolled in the clinical trial GOAL experienced at least 1 AE. A total of 869 AEs were reported (22.3 per patient). Thereof, 200 (23%) AEs were CTCAE grade 3/4, experienced by 37 (95%) of the 39 patients. 100 (12%) of the 869 AEs were documented as SAE, 31 (79%) patients experienced at least 1 SAE. 3 SAEs were assessed as related and unexpected (preferred terms (PT): hypertensive crisis, pulmonary oedema and angioedema) and therefore reported as SUSAR.

Most frequently the documented AEs belong to the following system organ classes (SOC): blood and lymphatic system disorders (246 (28%) AEs in 38 (97%) patients), general disorders and administration site conditions (131 (15%) AEs in 36 (92%) patients), gastrointestinal disorders (118 (14%) AEs in 34 (87%) patients), infections and infestations (55 (6%) AEs in 32 (82%) patients), respiratory, thoracic and mediastinal disorders (53 (6%) AEs in 29 (74%) patients), investigations (52 (6%) AEs in 19 (49%) patients) and skin and subcutaneous tissue disorders (49 (6%) AEs in 25 (64%) patients).

Treatment emergent AEs that were documented for at least 25 % of the BERT patients were (PTs): leukopenia (76 in 28 (72%) patients), thrombocytopenia (73 in 25 (64%) patients), neutropenia (41 in 20 (51%) patients, fatigue (39 in 25 (64%) patients), lymphopenia (35 in 16 (41%) patients), nausea (32 in 22 (56%) patients), mucosal inflammation (31 in 19 (49%) patients), pyrexia (22 in 14 (36%) patients), diarrhoea (20 in 15 (38%) patients), anaemia (16 in 11 (28%) patients), rash (16 in 11 (28%) patients), constipation (15 in 13 (33%) patients, cough (13 in 12 (31%) patients) and decreased appetite (12 in 10 (26%) patients).

The vast majority of the CTCAE grade 3/4 AEs occurred in SOC blood and lymphatic disorders (136 (68%) of 200 AEs in 34 (87%) patients), including (PTs) leukopenia (44 AEs in 22 (56%) patients), lymphopenia (35 AEs in 16 (41%) patients), thrombocytopenia (29 AEs in 14 (36%) patients, neutropenia (25 AEs in 18 (46%) patients) and anaemia (3 AEs in 3 (8%) patients).

Most of the reported SAEs belong to SOCs blood and lymphatic disorders (38 (38%) of 100 SAEs in 22 (56%) patients) and infections and infestations (18 (18%) of 100 SAEs in 11 (28%) patients). Most frequently the following SAEs were reported (PTs): lymphopenia (20 SAEs in 13 (33%) patients), thrombocytopenia (7 SAEs in 4 (10%) patients), leukopenia (5 SAEs in 5 (13%) patients), neutropenia (5 SAEs in 5 (13%) patients) and pyrexia (5 SAEs in 4 (10%) patients).

Overall the treatment was well tolerated and toxicity was within the expected range.

Conclusion:

The BeRT-combination of 50mg Temsirolimus (day 1, 8, 15) in combination with Bendamustine and Rituximab is a safe and feasible regimen with substantial activity. As mTOR inhibitors display a noticeable side effect profile especially with long term use the combination with a chemoimmunotherapy may be a suitable way of balancing efficacy and tolerability, thereby widening the therapeutic portfolio.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** April 06/2021

Print Name:

Signature: