Report Synopsis of Study :

A phase II trial to evaluate the safety, feasibility and efficacy of a salvage therapy consisting of the mTOR inhibitor Temsirolimus (Torisel™) added to the standard therapy of Rituximab and DHAP for the treatment of patients with relapsed or refractory diffuse large cell B-Cell lymphoma – the **STORM** trial

EudraCT-Nr.: 2011-001491-20

Vorlage-Nr.: 4038345

1) **Name of Sponsor/Company:**	4) **Individual Study Table Referring to Part of the Dossier:** n.a.[1]	*(For National Authority Use only)*
Ruprecht-Karls University Heidelberg, Medical Faculty *represented by Universitätsklinikum Heidelberg* *and its acting commercial director* *Mr. Hartmut Masanek* *Im Neuenheimer Feld 672* *69120 Heidelberg* *Delegated to the Medizinischen Klinik V* *Represented by the director* *Prof. Dr. C. Müller-Tidow* *Delegated to the CI* *Dr. Julia Meissner*	Volume: n.a. Page: n.a.	
2) **Name of Finished Product:** *Torisel®*		
3) **Name of Active Substance:** *Temsirolimus*		

5) **Title of Study[2]:**

*A phase II trial to evaluate the safety, feasibility and efficacy of a salvage therapy consisting of the mTOR inhibitor Temsirolimus (Torisel™) added to the standard therapy of Rituximab and DHAP for the treatment of patients with relapsed or refractory diffuse large cell B-Cell lymphoma – the **STORM** trial*

Phase-II-Studie zur Bewertung der Sicherheit, Durchführbarkeit und Wirksamkeit der Salvage-Therapie, mit dem mTOR-Hemmer Temsirolimus (Torisel ™) in Ergänzung zu der Standardtherapie bestehend aus Rituximab und DHAP zur Behandlung von Patienten mit rezidiviertem oder refraktärem diffusen großzelligem B-Zelllymphom - STORM-Studie -

First submission:	*Protocol Version 1.2 dated 13.09.2012 - Submission received approval*
Non-substantial Amendment:	*Protocol Version 1.3 dated 09.10.2012 - Changes in in- and exclusion criteria and specification of drug administration*
Non-Substantial Amendment:	*Protocol Version 1.4 dated 07.12.2012 - Change of the insurance company*
Amendment 1:	*Protocol Version 1.5 dated 16.12.2013 - Changes in conduct of the trial (i.a. concerning SPCs Torisel and MabThera)*
Amendment 2:	***Protocol Version 1.6 dated 23.05.2017 (Last Version) - Change of LKP***

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

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[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

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8) **Publication (reference):**

2015 Abstract: International Conference on Malignant Lymphoma (ICML) Lugano

2016 Abstract: American Society of Hematology (ASH) Annual Meeting in San Diego

2017 Abstract: International Conference on Malignant Lymphoma (ICML) Lugano

9) **Studied period (years)[3]:**	10) **Phase of development:** Phase II
Date of first enrolment: FPI 16.04.2013	
Date of last completed: LPLT 14.10.2016	

11) **Objectives:**

The STORM-trial consists of two parts.

***In the part I** (dose escalation of Temsirolimus) the primary objective is to establish a maximum tolerated dose of Temsirolimus in combination with Rituximab and DHAP. Secondary objective is to prove ability to mobilize stem cells in patients scheduled to high dose therapy.*

***In the part II** (full target dose) the primary objective is to evaluate the ORR in patients with relapsed DLBCL. The secondary objective is to evaluate PFS, OS and Toxicity.*

12) **Methodology:**

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

Eligible patients with histologically proven diagnosis of DLBCL according to the World Health Organization classification and with first or second relapse of DLBCL were included. After inclusion patients in part I of the trial received 2 to 4 cycles of 25 or 50 mg of Temsirolimus in combination with R-DHAP depending on the cohort they were admitted to.

All cohorts additionally received:
Rituximab (375 mg/m² day 2)
Dexamethasone 40 mg day 3-6
Cisplatin 100 mg/m² day 3
(Cisplatin could be replaced in the consecutive cycles by carboplatin AUC 5 if the patient experienced kidney toxicity in the previous cycle, i.e. decrease of creatinine clearance to 60 ml/min or lower.)

Cytarabine 2x2 g/m² day 4

In part II of the study patients received 2 to 4 cycles of the full target dose of Temsirolimus in combination with R-DHAP, established in the part I of the trial.

Special attention in part I and part II of the study was brought to monitoring of adverse events.

In both parts of the trial stem cell mobilization and subsequent high dose therapy and autologous stem cell transplantation could be performed in eligible patients. It was recommended to mobilize stem cells after the second treatment cycle with G-CSF starting on day 5.

Study procedures were divided into three periods (screening / baseline / pre-treatment, treatment and follow up).

Active treatment with Temsirolimus in combination with R-DHAP for 2 to 4 cycles lasted to a maximum of 104 days.

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

***Planned: In the Part I,** dose escalation part of this trial, a standardized design of 6 + 6 patients was planned for the establishment of the maximum tolerated dose of Temsirolimus in combination with R-DHAP. It was intended to include 6 patients in each dose level. 5 cohorts were planned administering up to a maximum of 4 cycles 25 mg (cohort A), 50 mg (cohort B), 75 mg (cohort C), 100 mg (cohort D) or 15 mg (cohort X) Temsirolimus at Day 1, 8 in combination with Rituximab and DHAP. It was intended that after inclusion of 6 patients, each patient had to receive at least 1 complete cycle without dose limiting toxicity until the enrolment into the next cohort could be initiated. A maximum of up to 48 patients in the Part I of the trial was possible.*

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

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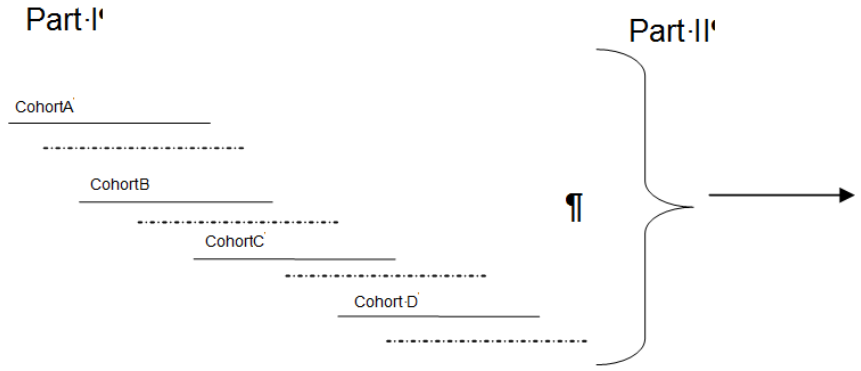

In total 15 patients were included in Part I of the study. 8 patients received a dose of 25 mg Temsirolimus per treatment administration (=per week), while 7 patients received 2-4 cycles of 50mg Temsirolimus in combination with R-DHAP per treatment administration.

Analyzed:

***In the Part II** of the trial it was planned to enroll 40 patients to receive the full target dose.*

38 patients were enrolled in Part II

53 patients were analyzed (15+ 38 patients, Part I+II combined)

53 patients were analyzed for safety and efficacy (Part I+II combined)

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

Diagnosis: Diffuse large B-cell lymphoma with documented relapse or progression following at least one but a maximum of two prior treatments.

Main criteria for inclusion:

- *Patients with histologically proven diagnosis of diffuse large cell B-cell lymphoma (DLBCL) according to the World Health Organization classification*
- *Documented relapse or progression following at least one treatment but a maximum of 2 prior treatments. Prior treatment must have included at least 3 cycles of anthracycline containing chemotherapy (e.g. CHOP-like)*
- *Any of the following: at least 1 measurable tumor mass (>1.5 cm x >1.0 cm), involvement of any organ or bone marrow infiltration*
- *Subjects 18 years or older*
- *Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study*
- *Adequate bone marrow reserve: Platelets of at least 75000/µl, absolute neutrophil count at least 1500/µl, Hemoglobin of at least 10 g/dl*
- *Alanine aminotransferase (ALT) < 2.5 x upper limit of normal (ULN); Aspartate aminotransferase (AST) < 2.5 x ULN*
- *Total bilirubin < 1.5 x ULN except chronic hepatic conditions leading to bilirubin increase but not interfering therapy, e. g. Gilbert´s Syndrom*
- *Calculated creatinine clearance (according to CKD-EPI, if possible) > 70 mL/min*
- *Eastern Cooperative Oncology Group [ECOG] performance Status < 3*
- *Female subject must be postmenopausal (for at least 6 months), surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study. Practicing an effective method of birth control as described above has to be continued for at least 12 month after end of treatment. Female subjects of childbearing age must have a negative serum ß-hCG pregnancy test at screening*
- *Male subject, if sexual active and with a sexual partner of childbearing age must be practicing an effective method of contraception throughout the study (e.g. surgical sterilization or double-barrier method. Prescription oral contraceptives, contraceptive injections, intrauterine device, surgically sterilization or contraceptive patch in female sexual partners).*

Practicing an effective method of birth control as described above has to be continued for at least 12 month after end of treatment.

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

Drug code:	*ATC: L01X E09*
International nonproprietary name (INN):	*Temsirolimus*
Registered trade name:	*Torisel®*
Formulation:	*Concentrate and solvent for solution for infusion (sterile concentrate)*
Manufacturer:	*PFIZER PHARMA GmbH*
Dosage authorized:	*Part I - Dose escalation: Starting dose of 25 mg Temsirolimus is stepwise escalated (each step with 25 mg Temsirolimus) up to a dose of 100 mg Temsirolimus* *Part II - Full target dose part of the Trial: Dose level established in part I.*
Mode of administration in the trial:	*intravenous*
Batch number:	*AJY8/1M, AJL2/9H, AJIA/96, AJL2/9A, AJL2/1S, AJL2/17, AJ64/1Z,*
AIIM/9V,	*AIEM/1Q, AIIM/12, AIEM/1X, AIEM/1N, AI3V/1U, AI3V/1M, AI3V/16, AHRE/1Q, AHC2/1I*

16) **Duration of treatment:**

In both parts *each treatment was repeated up to a maximum of 4 cycles. Duration of each cycle was 21 days. The treatment phase from first to last intake of study medication lasted to a maximum of 104 days.*

17) **Reference therapy, dose and mode of administration, batch number:**

Standard therapy of Rituximab and DHAP (Dexamethasone, High dose Arabinosid, Cisplatin) - Non-investigational medicinal products.
The Rituximab DHAP protocol (Rituximab 375 mg/m² day 1, Dexamethasone 40 mg day 3-6, Cisplatin 100 mg/m² day 3, Cytarabine 2x2 g/m² day 4, repeat day 22) is a standard salvage protocol for malignant lymphoma.

18) **Criteria for evaluation[4]:**

In Part I *the number of dose limiting toxicities (DLTs) were counted to determine the maximum tolerated dose of Temsirolimus.*

DLTs were defined as follows:

- *Any CTCAE grade V toxicity with an at least possible relationship to the trial treatment*
- *Any hematological toxicity not recovering to at least NCI CTCAE grade II after 28 days after start of the last STORM-cycle (except as a consequence of bone marrow insufficiency due to bone marrow infiltration). Lymphopenia is an expected toxicity in treatment with Rituximab and is not considered as DLT.*
- *Any non-hematological toxicity NCI CTCAE grade III/IV not recovering to grade II within 14 days after initial occurrence and with an at least possible relationship to the trial treatment*

Secondary endpoint was the number of successful stem cell mobilizations.

*In **Part II**, the primary endpoint was the rate of remission (CR, CRu) and rate of response (CR, CRu, PR) at end of last follow-up was analysed.*

Secondary endpoints (assessed at end of last follow-up except stem cell transplantations):

- *Progression-free survival*
- *Time to progression*
- *Overall survival*
- *Remission and response rates*
- *Number of high dose consolidation therapies and subsequent stem cell transplantations*

Safety

In order to assess the safety the frequency of adverse events and laboratory data were analysed.

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

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19) ***Statistical methods:***

Primary Analysis:

In Part I the number of dose limiting toxicities (DLTs) during the first two cycles and overall were counted to determine the maximum tolerated dose of Temsirolimus.

In Part II of the trial the primary analysis comprised overall response and remission rates after end of last follow-up, presented by descriptive statistics. Overall response was defined as complete response (CR or CRu) or partial response (PR) and overall remission as complete response (CR, CRu) at the respective time point based on International Working Group recommendations. For overall response assessments at the end of follow-up the last observation carried forward (LOCF) method was applied in case of missing values at the respective time point. 95% confidence intervals were given. As from published data with Rituximab in combination with DHAP a response rate of 60 – 65 % (40% CR and CRu) was assumed.

Secondary analyses:

In Part I the number of successful stem cell mobilizations was assessed.

In Part II progression-free survival (PFS), time to progression (TTP), overall survival (OS), at end of last follow up were determined for the combined data of Part I and Part II of the trial.

- *PFS was defined as time from treatment start until time of disease progression, relapse or death, whatever occurs first. In case of no event, PFS was censored at the time of last tumour evaluation.*
- *TTP was defined as time from treatment start until time of disease progression. In case of no event, TTP was censored at the time of last tumour evaluation.*
- *OS was defined as time from treatment start until death. In case of no event, OS was censored at the date of last patient contact.*

PFS, TTP and OS were presented by Kaplan-Meier curves. Patients with and without consolidating high dose therapy as well as patients with autologous and allogeneic stem cell derivation were compared by exploratory log-rank tests.

The number of successful transplantations after stem cell mobilization and subsequent high dose therapy was analyzed descriptively.

The efficacy statistics were descriptive for each group. Nominal and categorical data were displayed by absolute and relative frequencies. Continuous and quasi-continuous data were presented by number of observations (n), mean, standard deviation, median, minimum and maximum.

Patients from the first part of the trial were included into the analyses of the second part of the trial. Data from part I and II were analysed together as well as separated by the maximum dose of Temsirolimus the patients received (25 mg and 50 mg) which resulted in a group consisting of part I and part II patients who received 25mg Temsirolimus and a second group with patients who received 50 mg Temsirolimus. No hypothesis testing between the two dose groups was performed. Analyses were additionally performed separated by consolidating high dose therapy and type of stem cell therapy.

Safety analyses:

Special attention in Part I and Part II of the study was brought to monitoring of adverse events. Frequency of Adverse events were calculated. Adverse events were 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. Safety analyses were purely descriptive.

Populations:

All primary and secondary analyses were performed for the safety population and were repeated for the evaluable and the per protocol (PP) population. Safety analyses were performed in the safety population. The safety population comprised all subjects who signed the informed consent document and received at least 1 dose of study treatment. All subjects who had no major inclusion/exclusion violations, had measurable disease at baseline, received at least 1 dose of any study drug, and had at least 1 response assessment were included into the evaluable population. Major inclusion violations were defined as

- *No histologically proven diagnosis of diffuse large cell V-cell lymphoma (DLBCL) according to the World Health Organization classification*
- *No documented relapse or progression following at least one treatment but a maximum of prior 2 treatments*
- *None of the following: at least one measurable tumor mass (>1.5 cm x 1.0 cm), involvement of any organ or bone marrow infiltration*
- *No adequate bone marrow reserve: Platelets of at least 75000/µl, absolute neutrophil count at least 1500/µl, hemoglobin of at least 10g/dl*

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The PP population was defined as all subjects from the evaluable population treated at the predefined maximum tolerated dose (MTD=25mg) in all cycles.

20) **Summary – Conclusions[5]:** Temsirolimus can be safely added to DHAP and Rituximab with promising activity

Part I: Disposition and baseline characteristics

In total 15 patients (pts) were included in part I of the study. 8 patients received a dose of 25 mg Temsirolimus per treatment administration (=per week), while 7 patients received 2-4 cycles of 50mg Temsirolimus in combination with R-DHAP per treatment administration.

Median age was 70 (range 49-76) years and median number of prior regimen was 1.

Part I: Results

Two formal dose-limiting toxicities (DLTs; one esophagus infection in the 50 mg cohort, one venous thrombosis in the 25mg cohort) were observed. The most frequent non-hematologic side effects were nausea (9 pts, 60 %), epistaxis (7 pts, 47 %), fatigue (6 pts, 40 %), increased ALT (6 pts, 40 %), increased creatinine (6 pts, 40 %). Frequent grade 3/4 events (n>2) in both cohorts (25 mg/ 50 mg) were leukopenia (11 pts, 73 %, mean duration 4.4 - 6.7 days), thrombocytopenia (11 pts, 73%, mean duration of 4.6- 11.9 days), lymphopenia (6 pts, 40 %), anemia (5 pts, 33 %), neutropenia (3 pts, 20 %), renal failure (3 pts, 20 %) and infections (4 pts, 27 %, bladder infection, Esophagus infection, port infection, soft tissue infection, mucositis).

Response data of Part I and the number of stem cell mobilizations and subsequent transplantations were evaluated together with the data of Part II.

Part I: Conclusion

For the Part II proportion of the trial, Temsirolimus at 25mg on day 1 and 8 was determined as recommended dose. Temsirolimus can be safely added to DHAP and Rituximab with promising activity.

Part I+II: Disposition and baseline characteristics

All 38 patients of Part II received the MTD of 25 mg Temsirolimus as determined in Part I of the study.

When combining part I and part II of the study, 53 patients were enrolled. All patients received at least one dose of study medication; hence the safety population comprised 53 patients as well. 43 patients were assigned to the evaluable population and 27 patients were included in the PP population.

35 patients completed the study regularly. Main reason for irregular end of treatment were toxicities or because the patient or the physician requested it (5 pts, respectively, 9.4%). 24 patients had a regular end of the study while the main reason for an irregular end was the death of the patient (21 pts, 39.6 %)

33 patients (62 %) were male, median age of the study population was 63 years (Q1-Q3: 54-63 years).

Part I+II: Concomitant diseases and therapies:

All patients except one (98%) had concomitant diseases. Most abundant were

- Vascular disorders (28 pts, 53%), most frequently hypertension (21 pts, 40%),
- Metabolism and nutrition disorders (20 pts, 38%), most frequently Type 2 diabetes mellitus (7 pts, 13 %),
- Gastrointestinal disorders (20 pts, 38%),
- Blood and lymphatic system disorders (19 pts, 36%), most frequently anaemia (11 pts, 21%) and lymphopenia (11 pts, 21%),
- Musculoskeletal and connective tissue disorders (19 pts, 36%) and
- Nervous system disorders (19 pts, 36%), most frequently polyneuropathy (12 pts; 23%).

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

Part I+II: Concomitant medication (pre-medication)

51 patients (96%) received medication before the start of the trial. Most frequent were

- Antihistamines for systemic use (50 pts, 94%), most frequently substituted alkylamines (41 pts, 77%)
- Antiemetics and antinauseants (47 pts, 89%), especially serotonin (5HT3) antagonists (47 pts, 89%),
- Analgesics (47 pts, 89%; all of them anilides) and
- Drugs for acid related disorders (43 pts, 81%), especially H2-receptor antagonists (43 pts, 81%).

Part I+II: Concomitant medication (G-CSF and non G-CSF)

All pts received G-CSF.

Most frequent (non G-CSF) medication was

- Drugs for acid related disorders (53 pts, 100%), mainly proton pump inhibitors (53 pts, 100%),
- Antibacterials for systemic use (53% pts, 100%)
- Drugs for functional gastrointestinal disorders (47 pts, 89%), especially propulsives (47 pts, 89%),
- Antithrombotic agents (45 pts, 85%), especially agents from the heparin group (43 pts, 81%)
- Analgesics (43 pts, 81%), especially pyrazolones (32 pts, 60%) and anilides (31 pts, 58%)

Part I+II: Exposure

19 patients completed 2 or 3 cycles, respectively. Median treatment duration measured from first day to last day of treatment was 51.6 days. On average 5 doses (à 25 or 50mg) of Temsirolimus were given (table 1).

Table 1: Exposure (Safety population)

Variable	Value	50mg Temsirolismus (Part I) (N=6)	25mg Temsirolismus (Part I+II) (N=47)	Total (N=53)
Completed cycles	0	0 (0%)	2 (4%)	2 (4%)
	1	1 (17%)	6 (13%)	7 (13%)
	2	1 (17%)	18 (38%)	19 (36%)
	3	4 (67%)	15 (32%)	19 (36%)
	4	0 (0%)	6 (13%)	6 (11%)
Total duration of study treatment [days]	N	6	47	53
	Mean	68.0	49.5	51.6
	SD	32.8	23.1	24.7
	Min	8	6	6
	Q1	55	32	33
	Median	80.5	53.0	55.0
	Q3	84	68	70
	Max	100	104	104
Number / days of Temsirolimus administration	N	6	47	53
	Mean	6.5	5.0	5.2
	SD	2.5	1.8	2.0
	Min	2	1	1
	Q1	5	4	4
	Median	8.0	5.0	5.0
	Q3	8	6	6
	Max	8	8	8
	Missing	0	0	0

Total dose intake Temsirolimus [mg]	N	6	47	53
	Mean	325.0	123.5	146.3
	SD	125.5	46.4	87.0
	Min	100	25	25
	Q1	250	100	100
	Median	400.0	100.0	125.0
	Q3	400	150	150
	Max	400	200	400

Missing values are not included in calculation of percentages.

Part I+II: Efficacy results:

Primary analysis: Response and remission rates

Safety population: The overall response rate at end of last follow-up was 72% (36 pts) with a 95% confidence interval of 59.55-84.45% (table 2). Complete response as best response until the end of last follow-up was achieved by 21 patients (42%). The remission rate was 42 [28.32; 55.68] %.

Patients with high dose consolidation therapy showed an overall response rate of 93% (26 pts out of 28) while patients without high dose therapy had a response rate of only 45% (10 pts out of 22 pts with data available). Remission rates were 61% (17 pts) in patients with high dose consolidation therapy vs. 18% (4 pts) without high-dose therapy. Patients with autologous stem cell derivation had a response rate of 91% (21 out of 23 pts with data available) and a remission rate of 65% (15 pts).

Evaluable and PP population: Sensitivity analyses showed a response rate of 72 % (31 out of 43 pts) in the evaluable population and a response rate of 70% (19 out of 27 pts) in the PP population (data not shown). Remission rates were 42% (18 pts) in the evaluable population and 37% (10 pts) in the PP population. Hence these analyses are consistent to the analyses in the safety population.

Table 2: Response and remission rates (Safety population)

Variable	Value	50mg Temsirolismus (Part I) (N=6)	25mg Temsirolismus (Part I+II) (N=47)	Total (N=53)
Overall response at end of Follow-up	Yes	4 (80%)	32 (71%)	36 (72%)
	No	1 (20%)	13 (29%)	14 (28%)
	Missing	1	2	3
	95% Lower Confidence Limit			0.5955
	95% Upper Confidence Limit			0.8445
Best response until end of Follow-up	CR (Complete Response)	4 (80%)	17 (38%)	21 (42%)
	CRu (Complete Response, unconfirmed)	0 (0%)	0 (0%)	0 (0%)
	PR (Partial Response)	0 (0%)	15 (33%)	15 (30%)
	SD (Stable Disease)	0 (0%)	2 (4%)	2 (4%)
	PD (Progressive Disease)	1 (20%)	11 (24%)	12 (24%)
	Missing	1	2	3
Remission at end of Follow-up	Yes	4 (80%)	17 (38%)	21 (42%)
	No	1 (20%)	28 (62%)	29 (58%)
	Missing	1	2	3
	95% Lower Confidence Limit			0.2832
	95% Upper Confidence Limit			0.5568

Patients with high dose consolidation therapy				
Overall response at end of Follow-up	Yes	2 (100%)	24 (92%)	26 (93%)
	No	0 (0%)	2 (8%)	2 (7%)
	95% Lower Confidence Limit			0.8332
	95% Upper Confidence Limit			1.0000
Remission at end of Follow-up	Yes	2 (100%)	15 (58%)	17 (61%)
	No	0 (0%)	11 (42%)	11 (39%)
	95% Lower Confidence Limit			0.4262
	95% Upper Confidence Limit			0.7880
Patients without high dose consolidation therapy:				
Overall response at end of Follow-up	Yes	2 (67%)	8 (42%)	10 (45%)
	No	1 (33%)	11 (58%)	12 (55%)
	95% Lower Confidence Limit			0.2465
	95% Upper Confidence Limit			0.6626
Remission at end of Follow-up	Yes	2 (67%)	2 (11%)	4 (18%)
	No	1 (33%)	17 (89%)	18 (82%)
	95% Lower Confidence Limit			0.0206
	95% Upper Confidence Limit			0.3430
Patients with autologous stem cell transplantation:				
Overall response at end of Follow-up	Yes	2 (100%)	19 (90%)	21 (91%)
	No	0 (0%)	2 (10%)	2 (9%)
	95% Lower Confidence Limit			0.7979
	95% Upper Confidence Limit			1.0000
Remission at end of Follow-up	Yes	2 (100%)	13 (62%)	15 (65%)
	No	0 (0%)	8 (38%)	8 (35%)
	95% Lower Confidence Limit			0.4575
	95% Upper Confidence Limit			0.8468

Missing values are not included in calculation of percentages.
Response: CR, CRu, PR
Remission: CR, CRu

Secondary analyses

Stem cell mobilization and transplantation

Stem cells were mobilized in 40 patients (78%) of which 38 patients (95%) had a successful mobilization (table 3). 85% (29 pts) had an autologous stem cell derivation and 15% (5 pts) an allogeneic stem cell derivation. For 6 patients no information was available on the type of stem cell extraction. In all cases of autologous stem cell derivation, cells were extracted from peripheral blood. High dose consolidation therapy and subsequent stem cell transplantation was performed in 28 patients (53% of the total population and 97% of the patients with stem cell extraction).

Regarding patients with confirmed autologous stem cell derivation only, 97% (28 pts) had a successful stem cell mobilization and 79% (23 pts) had a high dose consolidation therapy and a subsequent stem cell transplantation.

Table 3: Stem cell mobilization and transplantation (Safety population)

Variable	Value	50mg Temsirolismus (Part I) (N=6)	25mg Temsirolismus (Part I+II) (N=47)	Total (N=53)
Stem Cell Mobilization During Storm Therapy	Yes	4 (80%)	36 (78%)	40 (78%)
	No	1 (20%)	10 (22%)	11 (22%)
	Missing	1	1	2
Successful mobilization	Yes	3 (75%)	35 (97%)	38 (95%)
	No	1 (25%)	1 (3%)	2 (5%)
Stem cell derivation	Autologous	3 (100%)	26 (84%)	29 (85%)
	Allogeneic	0 (0%)	5 (16%)	5 (15%)
	Missing	1	5	6
If autologous	Peripheral blood	3 (100%)	26 (100%)	29 (100%)
	Bone marrow	0 (0%)	0 (0%)	0 (0%)
High dose consolidation therapy performed	Yes	2 (33%)	26 (55%)	28 (53%)
	No	4 (67%)	21 (45%)	25 (47%)
	Missing	0	0	0
Autologous stem cell derivation				
Stem Cell Mobilization During Storm Therapy	Yes	3 (100%)	26 (100%)	29 (100%)
Successful mobilization	Yes	2 (67%)	26 (100%)	28 (97%)
	No	1 (33%)	0 (0%)	1 (3%)
Stem cell transplantation performed?	Yes	2 (67%)	21 (81%)	23 (79%)
	No	1 (33%)	5 (19%)	6 (21%)
Allogeneic stem cell derivation				
Stem Cell Mobilization During Storm Therapy	Yes	0 (0%)	5 (100%)	5 (100%)
Successful mobilization	Yes	0 (0%)	5 (100%)	5 (100%)
Stem cell transplantation performed	Yes	0 (0%)	5 (100%)	5 (100%)

Missing values are not included in calculation of percentages.

Progression-free survival

Data for 47 patients were available (figure 1). Median progression-free survival times for the complete study population could not be determined as less than 50% of the patients had a disease progression. The lower 95% confidence limit was 154 days.

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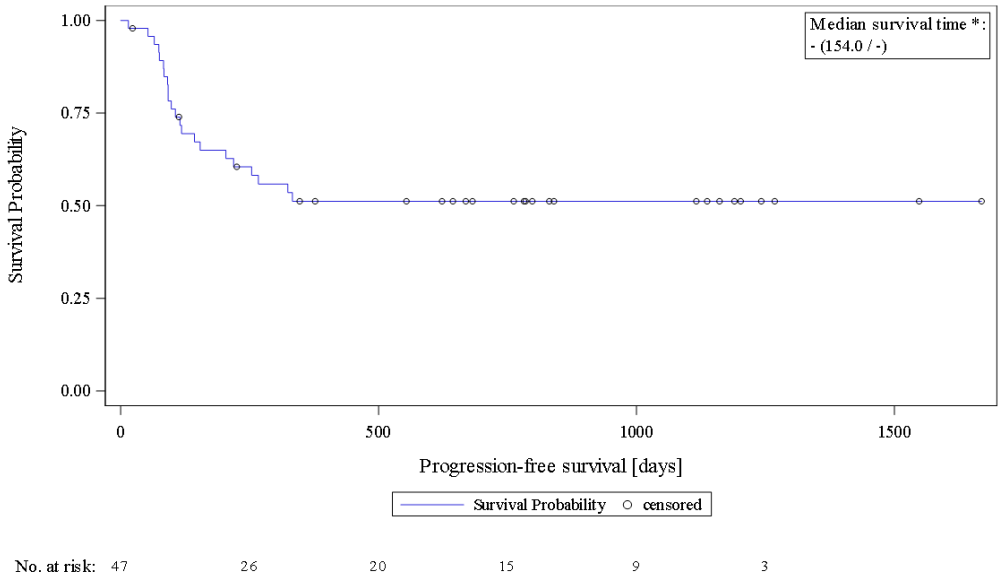

Figure 1: Progression-free survival (Safety population)

When separated by high dose consolidation therapy, a significant difference between the patients with and patients without high dose consolidation therapy was observed (p<0.0001; figure 2a). The median progression-free survival time was 98 days in the group without high dose therapy, while the median progression free survival could not be determined in the group that received a high dose consolidation therapy.

Progression-free survival separated by autologous vs. allogeneic stem cell derivation differs significantly between the two groups (p<0.0001) though it should be regarded that only in 4 patients an allogeneic stem cell derivation was performed (figure 2b).

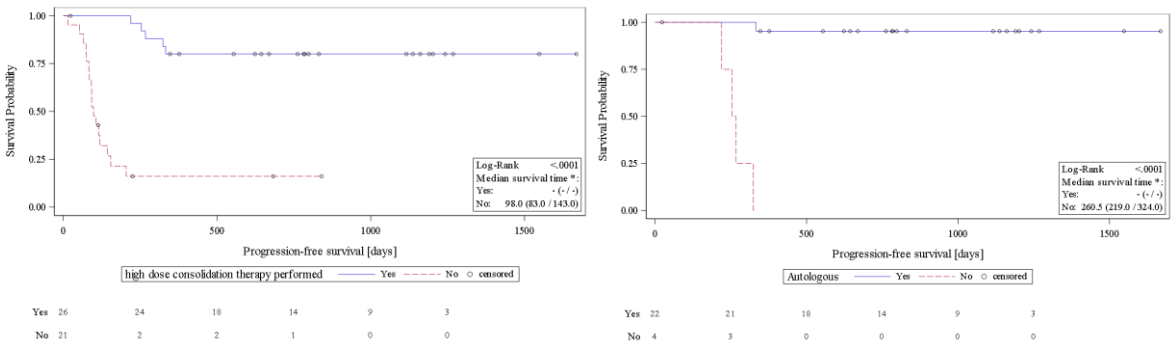

Figure 2a/b: Progression-free survival separated by high-dose consolidation therapy (left) and autologous/ allogeneic stem cell derivation (right) (Safety population)

Analyses of progression-free survival in the evaluable population and in the PP population were consistent with the analyses in the safety population (data not shown).

Time to progression

The median time to progression could not be determined (figure 3). The lower 95% confidence limit was 204 days.

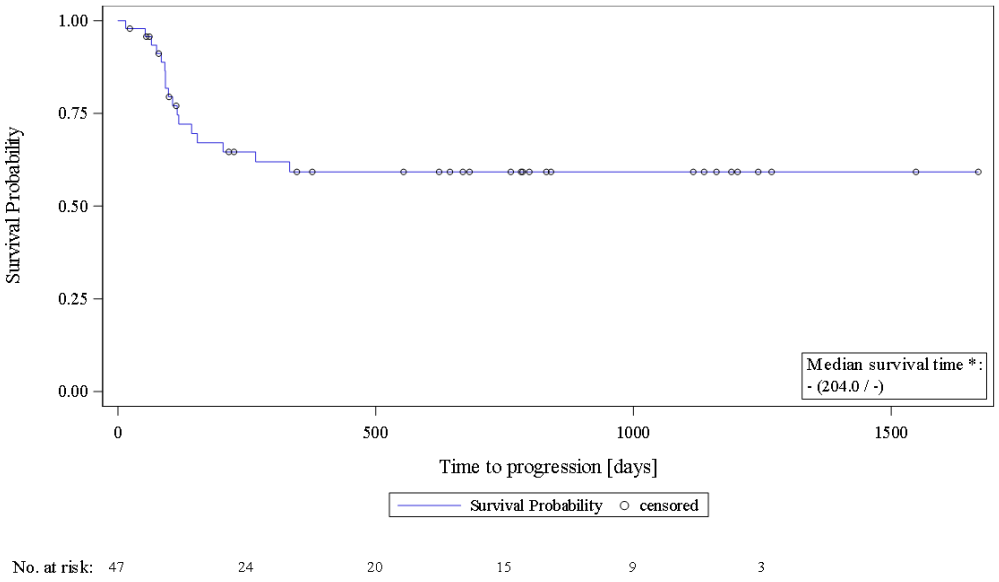

Figure 3: Time to progression (Safety population)

Patients who received a high dose consolidation therapy showed a significantly better outcome than patients without high dose therapy did (p<0.0001). The median time to progression for patients without high dose consolidating therapy was 106 [84; 154] days (figure 4a).

Time to progression differed significantly between patients with and patients without allogeneic stem cell derivation (p<0.0001) though data are sparse for patients with allogeneic stem cell derivation (figure 4b). The median time to progression for patients with allogeneic stem cell derivation was 267 days.

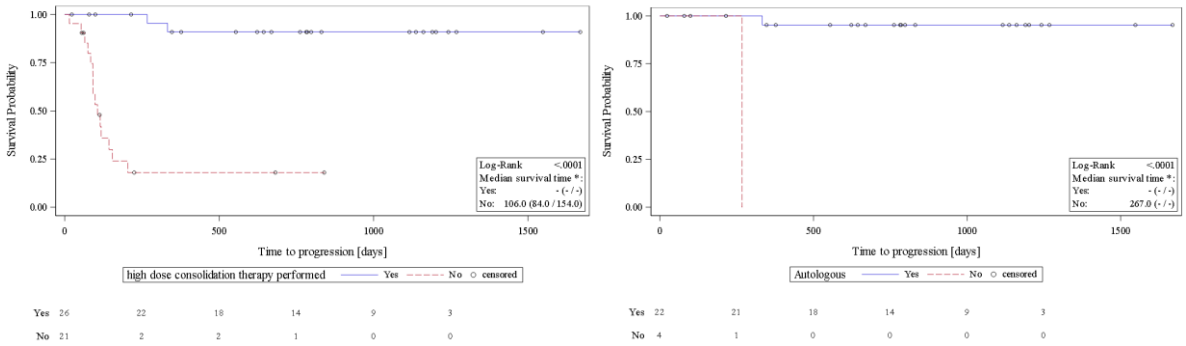

Figure 4a/b: Time to progression separated by high-dose consolidation therapy (left) and autologous/ allogeneic stem cell derivation (right; Safety population)

Analyses of the time to progression in the evaluable population and in the PP population were consistent with the analyses in the safety population (data not shown).

Overall survival

Data for 52 patients were available. The median survival time for the complete population could not be determined (figure 5). The lower confidence limit was 324 days.

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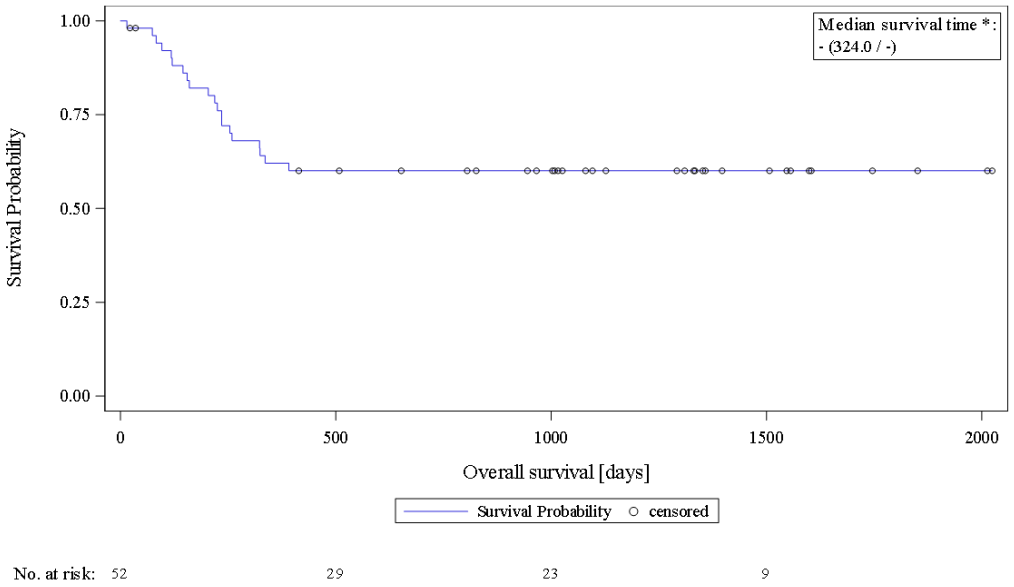

Figure 5: Overall survival (Safety population)

The overall survival time differed significantly between patients with and without high dose consolidation therapy and between patients with autologous vs. allogeneic stem cell derivation (p<0.0001, respectively; figure 6a). Median survival time for patients without high dose consolidation therapy was 235 [145;336] days, for patients with allogeneic stem cell derivation 289 [219; -] days. Median survival times could neither be calculated for patients with high dose therapy nor for patients with autologous stem cell production (figure 6b).

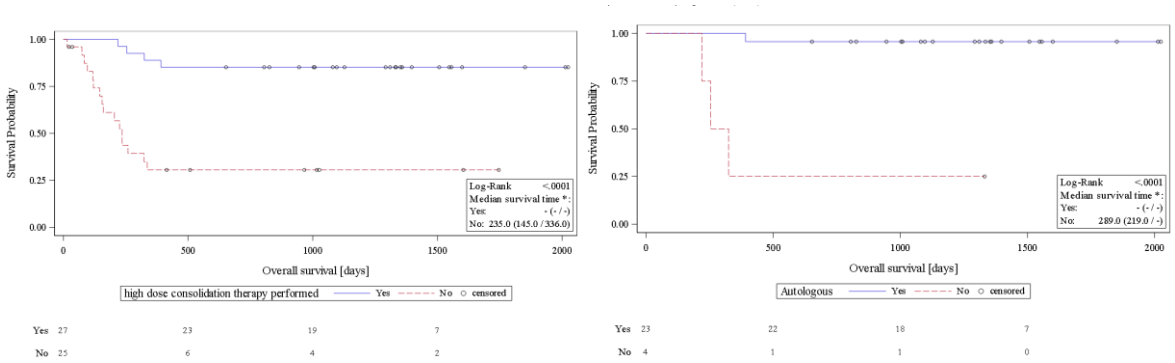

Figure 6a/b: Overall survival separated by high-dose consolidation therapy (left) and autologous/ allogeneic stem cell derivation (right; Safety population)

Analyses of overall survival in the evaluable population and the PP population were consistent with the analyses in the safety population (data not shown).

Summary concerning efficacy

The overall reponse rate at end of last follow-up was 72% with a 95% confidence interval of 59.55-84.45%. The remission rate was 42% [28.32; 55.68]. Patients with high dose consolidation therapy displayed much higher response rates than patients without high dose therapies (93% vs. 45%).

Autologous stem cell mobilization was performed in 29 patients with a mobilization success of 97%. 79% had a subsequent stem cell transplantation.

The probabilities for progression-free survial, time to progression and overall survival were above 50% in the safety population. Exploratory tests showed statistically striking differences between patients with and without high-dose consolidation therapy as well as between patients with autologous vs. allogeneic stem cell transplantation with a better outcome for patients with high-dose consolidation therapy and autologous stem cell derivation.

Sensitivity analyses in the evaluable and the per protocol population concerning response and remission rates as well as time-to-event data delivered consistent results.

Safety results:

All AEs were documented on the appropriate pages of the CRF and coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. The relatedness between each event and the administration of study medication was judged according to modified WHO criteria. AEs assessed with "certain", "probable" or "possible" causal relationship to study medication were graded as adverse reactions, AEs assessed as "unlikely" or "not related" were considered as not related to study medication. Seriousness was defined according to the Seriousness Criteria of Good Clinical Practice Guideline (GCP). Severity assessment was performed in accordance with National Cancer Institute common terminology criteria for adverse events (CTCAE) Version 4.03. The following table shows an overview of the reported AEs.

Table 4: Overview of reported AEs

	50 mg Temsirolimus (Part I)		**25 mg Temsirolimus (Part I and II)**		**Total**	
Patients with	**Patients (N=6)**	**AEs (nAE=253)**	**Patients (N=47)**	**AEs (nAE=1425)**	**Patients (N=53)**	**AEs (nAE=1678)**
at least one AE	6 (100%)	253 (100%)	47 (100%)	1425 (100%)	53 (100%)	1678 (100%)
at least one serious AE	6 (100%)	15 (6%)	37 (79%)	87 / 85* (6% / 6%)	43 (81%)	102 / 100* (6% / 6%)
at least one related AE **before** sponsor's assessment	6 (100%)	190 (75%)	47 (100%)	873 (61%)	53 (100%)	1063 (63%)
at least one related AE **after** sponsor's assessment	6 (100%)	190 (75%)	47 (100%)	878** (62%)	53 (100%)	1068** (64%)
at least one related serious AE **before** sponsor's assessment	5 (83%)	9 (4%)	26 (55%)	51 (4%)	31 (58%)	60 (4%)
at least one related serious AE **after** sponsor's assessment	5 (83%)	9 (4%)	27** (57%)	56** (4%)	32** (60%)	65** (4%)

*For SAE "renal function test abnormal" (MedDRA preferred term (PT), patient 0206) there were 3 corresponding AEs documented in the study database by the study team. Therefore, there are only 100 SAEs in the safety database with 102 corresponding AEs in the study database.

**There were 5 SAEs (MedDRA preferred terms (PTs): "acute kidney injury" (patient 0823 and 0727), "epistaxis" (patient 0941 and 0943) and "pyrexia" (patient 0153)) which were classified as not related to study medication (SAE) by the investigator whereas the sponsor assessed them as related to study medication (SAR). Taking both assessments into consideration these 5 SAEs were additionally classified as SARs. So there occurred 1068 ADRs and 65 SARs in the clinical trial.

Adverse Events:

All patients reported at least one AE. A total of 1678 AEs were reported (32 per pat.). Thereof, 253 AEs (15%, 42 per pat.) occurred in the group of patients treated with 50 mg Temsirolimus and 1425 AEs (85%, 30 per pat.) occurred in in the group of patients treated with 25 mg Temsirolimus. The following table shows the number of AEs allocated to MedDRA system organ classes (SOCs) and treatment group.

Table 5: AEs allocated to MedDRA system organ classes (SOCs)

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	50 mg Temsirolimus (Part I)		25 mg Temsirolimus (Part I and II)		Total	
System Organ Class	**Patients (N=6)**	**AEs (nAE=253)**	**Patients (N=47)**	**AEs (nAE=1425)**	**Patients (N=53)**	**AEs (nAE=1678)**
Infections and infestations	5 (83%)	15 (6%)	27 (57%)	38 (3%)	32 (60%)	53 (3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0%)	0 (0%)	2 (4%)	2 (0%)	2 (4%)	2 (0%)
Blood and lymphatic system disorders	6 (100%)	78 (31%)	45 (96%)	408 (29%)	51 (96%)	486 (29%)
Immune system disorders	0 (0%)	0 (0%)	2 (4%)	2 (0%)	2 (4%)	2 (0%)
Endocrine disorders	2 (33%)	2 (1%)	2 (4%)	2 (0%)	4 (8%)	4 (0%)
Metabolism and nutrition disorders	4 (67%)	10 (4%)	37 (79%)	134 (9%)	41 (77%)	144 (9%)
Psychiatric disorders	2 (33%)	4 (2%)	20 (43%)	29 (2%)	22 (42%)	33 (2%)
Nervous system disorders	5 (83%)	12 (5%)	38 (81%)	92 (6%)	43 (81%)	104 (6%)
Eye disorders	3 (50%)	3 (1%)	12 (26%)	14 (1%)	15 (28%)	17 (1%)
Ear and labyrinth disorders	1 (17%)	1 (0%)	13 (28%)	17 (1%)	14 (26%)	18 (1%)
Cardiac disorders	1 (17%)	1 (0%)	10 (21%)	17 (1%)	11 (21%)	18 (1%)
Vascular disorders	3 (50%)	4 (2%)	17 (36%)	21 (1%)	20 (38%)	25 (1%)
Respiratory, thoracic and mediastinal disorders	2 (33%)	7 (3%)	32 (68%)	63 (4%)	34 (64%)	70 (4%)
Gastrointestinal disorders	5 (83%)	32 (13%)	43 (91%)	210 (15%)	48 (91%)	242 (14%)
Skin and subcutaneous tissue disorders	2 (33%)	4 (2%)	26 (55%)	43 (3%)	28 (53%)	47 (3%)
Musculoskeletal and connective tissue disorders	1 (17%)	1 (0%)	20 (43%)	34 (2%)	21 (40%)	35 (2%)
Renal and urinary disorders	4 (67%)	4 (2%)	19 (40%)	25 (2%)	23 (43%)	29 (2%)
Reproductive system and breast disorders	1 (17%)	1 (0%)	3 (6%)	3 (0%)	4 (8%)	4 (0%)

General disorders and administration site conditions	5 (83%)	13 (5%)	39 (83%)	124 (9%)	44 (83%)	137 (8%)
Investigations	5 (83%)	59 (23%)	35 (74%)	132 (9%)	40 (75%)	191 (11%)
Injury, poisoning and procedural complications	1 (17%)	2 (1%)	10 (21%)	14 (1%)	11 (21%)	16 (1%)
Surgical and medical procedures	0 (0%)	0 (0%)	1 (2%)	1 (0%)	1 (2%)	1 (0%)

Adverse Events considered as related to study medication (ADRs):

In 1063 (63%, 20 per pat.) of all AEs at least a possible causal relationship was assessed by the investigator between the occurrence of the AE and the administration of study medication. In addition, there were 5 SAEs (MedDRA preferred terms (PTs): “acute kidney injury” (patient 0823 and 0727), “epistaxis” (patient 0941 and 0943) and “pyrexia” (patient 0153)) which were classified as not related to study medication (SAE) by the investigator whereas the sponsor assessed them as related to study medication (SAR) during sponsor’s SAE assessment. Therefore, there were 1068 AEs (64%, 20 per pat.) with at least a possible causal relationship to study medication. 190 (18%, 32 per pat.) of these adverse drug reactions (ADRs) occurred in the group of patients treated with 50 mg Temsirolimus and 878 (82%, 19 per pat.) occurred in the group of patients treated with 25 mg Temsirolimus.

In the group of patients treated with 50 mg Temsirolimus, the MedDRA system organ classes (SOCs) in which most ADRs occurred were: “blood and lymphatic system disorders” (73 ADRs (38%) in 6 pts.), “investigations” (57 ADR (30%) in 5 pts.) and “gastrointestinal disorders” (20 ADR (11%) in 5 pts.). In the group of patients treated with 25 mg Temsirolimus, the MedDRA system organ classes (SOCs) in which most ADRs occurred were “blood and lymphatic system disorders” (336 ADR (38%) in 42 pts.) and “gastrointestinal disorders” (141 ADR (16%) in 35 pts.).

Severity of Adverse Events:

For severity analysis CTCAE grade 1 was classified as mild, CTCAE grade 2 as moderate and CTCAE grade >2 as severe. The severity assessment was missing for 7 adverse events. 701 (42%) of all AEs were judged as mild, 432 (26%) as moderate and 538 (32%) as severe. 99 (18%, 17 per pat.) of the 538 severe AEs occurred in the group of patients treated with 50 mg Temsirolimus and 439 (82%, 9 per pat.) in the group of patients treated with 25 mg Temsirolimus. 416 of the severe AEs were assessed as related to the study medication.

Serious Adverse Events:

In summary, 102 AEs were judged as serious and documented in the study database but there were only 100 reported SAEs in the safety database. The reason is that for 1 SAE (patient 0206, MedDRA preferred term (PT): “renal function test abnormal”, not related to study medication) there were 3 corresponding AEs documented by the study team. The SAE covers the period of seriousness of all 3 AEs. Therefore, there are only 100 SAEs (6%, 2 per pat.) in the safety database with 102 corresponding AEs in the study database. 15 (15%, 3 per pat.) of the serious adverse events (SAEs) occurred in the group of patients treated with 50 mg Temsirolimus and 85 (85%, 2 per pat.) occurred in the group of patients treated with 25 mg Temsirolimus.

65 SAEs were judged as related to the study medication. 5 of these 65 SARs were classified as not related to study medication by the investigator whereas the sponsor assessed them as related to study medication (SAR) during Sponsor’s SAE assessment. Therefore there are 5 SARs (MedDRA preferred terms (PTs): “acute kidney injury” (patient 0823 and 0727), “epistaxis” (patient 0941 and 0943) and “pyrexia” (patient 0153)) in the safety database whose corresponding AEs in the study database are assessed as not related to study medication. 9 (14%, 2 per pat.) of the serious adverse reactions (SARs) occurred in the group of patients treated with 50 mg Temsirolimus and 56 (86%, 1 per pat.) occurred in the group of patients treated with 25 mg Temsirolimus.

3 of these 65 SARs were assessed as unexpected by the sponsor (SUSAR) and were therefore reported to the competent authority, ethics committee and all investigators (MedDRA preferred terms (PTs): “left ventricular dysfunction (patient 0711, 50 mg Temsirolimus), „colitis“ (patient 0727, 25 mg Temsirolimus), „neutropenic sepsis“ (patient 0221, 25 mg Temsirolimus)).

The MedDRA system organ class (SOC) with most SAEs was “blood and lymphatic system disorders” (21 SAEs). The following SAEs (MedDRA preferred terms (PTs)) were reported: “febrile neutropenia” (7 pts.), “thrombocytopenia” (5 pts.), “febrile bone marrow aplasia” (3 pts.), “neutropenia” (2 pts.), “pancytopenia” (2 pts.) and “leukostasis syndrome” (1 pt.)

The following table shows the number of SAEs and SARs allocated to MedDRA system organ classes (SOCs) and treatment group:

Table 6: SAEs and SARs allocated to MedDRA system organ classes (SOCs)

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System Organ Class	**SAEs (N=15)**	**Related SAEs (N=9)**	**SAEs (N=85)**	**Related SAEs (N=56)**	**SAEs (N=100)**	**Related SAEs (N=65)**
Infections and infestations	5 (33%)	5 (56%)	7 (8%)	6 (11%)	12 (12%)	11 (17%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Blood and lymphatic system disorders	4 (27%)	1 (11%)	17 (20%)	15 (27%)	21 (21%)	16 (25%)
Immune system disorders	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Metabolism and nutrition disorders	0 (0%)	0 (0%)	6 (7%)	5 (9%)	6 (6%)	5 (8%)
Psychiatric disorders	0 (0%)	0 (0%)	1 (1%)	1 (2%)	1 (1%)	1 (2%)
Nervous system disorders	0 (0%)	0 (0%)	3 (4%)	1 (2%)	3 (3%)	1 (2%)
Ear and labyrinth disorders	1 (7%)	0 (0%)	2 (2%)	0 (0%)	3 (3%)	0 (0%)
Cardiac disorders	1 (7%)	1 (11%)	1 (1%)	0 (0%)	2 (2%)	1 (2%)
Vascular disorders	0 (0%)	0 (0%)	3 (4%)	2 (4%)	3 (3%)	2 (3%)
Respiratory, thoracic and mediastinal disorders	1 (7%)	0 (0%)	6 (7%)	4 (7%)	7 (7%)	4 (6%)
Gastrointestinal disorders	1 (7%)	1 (11%)	11 (13%)	8 (14%)	12 (12%)	9 (14%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	1 (1%)	1 (2%)	1 (1%)	1 (2%)
Renal and urinary disorders	1 (7%)	1 (11%)	15 (18%)	7 (13%)	16 (16%)	8 (12%)
General disorders and administration site conditions	0 (0%)	0 (0%)	6 (7%)	5 (9%)	6 (6%)	5 (8%)
Investigations	1 (7%)	0 (0%)	3 (4%)	1 (2%)	4 (4%)	1 (2%)
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)

Deaths:

In this clinical trial 3 SAEs with fatal outcome were reported (MedDRA preferred terms (PTs): Non-Hodgkin's lymphoma (SAE,

patient 0128), cerebral haemorrhage (SAR, patient 0727), neutropenic sepsis (SUSAR, patient 0221)). All 3 patients were in the group of patients treated with 25 mg Temsirolimus.

Summary concerning safety:

In summary, in this clinical trial 32 (10 severe) adverse events (AEs) per patient, 2 serious adverse events (SAEs) per patient and 1 serious adverse drug reaction (SAR) per patient were reported to the sponsor.

There were 42 adverse events (AEs) per patient in the group of patients treated with 50 mg Temsirolimus and 30 adverse events (AEs) per patient in the group of patients treated with 25 mg Temsirolimus.

3 serious adverse events (SAEs) per patient and 2 serious adverse drug reactions (SARs) per patient were reported in the group of patients treated with 50 mg Temsirolimus. In the group of patients treated with 25 mg Temsirolimus 2 serious adverse events (SAEs) per patient and 1 serious adverse drug reaction (SAR) per patient were reported to the sponsor."

Conclusion:

Temsirolimus can be safely added to DHAP and Rituximab with promising activity for the treatment of patients with relapsed or refractory diffuse large cell B-Cell lymphoma.

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

21) **Date of the report:** 23.10.2019

Print Name: Dr. Julia Meissner

Signature: