Safety and clinical activity of Temsirolimus in combination with Rituximab and DHAP for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma - the STORM trial

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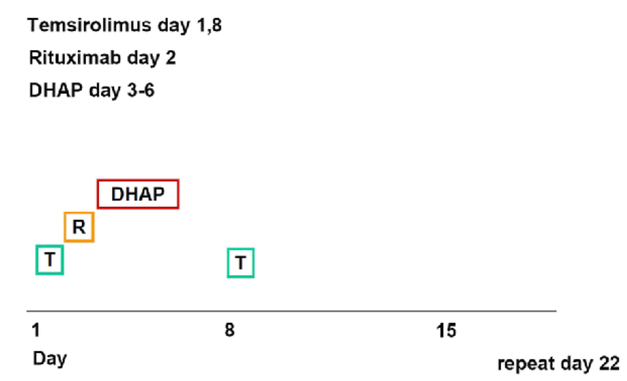
Background:
The current standard treatment of patients with relapsed or refractory diffuse large cell B-Cell lymphoma (DLBCL) primarily consists of intensified salvage therapy and, if the disease is chemo-sensitive, high dose therapy followed with autologous stem cell transplantation. In the rituximab era however, this treatment approach has shown only limited benefit. In particular, patients relapsing after rituximab-containing primary treatment have an adverse prognosis, especially if this occurs within the first year after therapy or if the disease is primarily refractory. Therefore there is an ultimate need for improved salvage treatment approaches. Recently, the specific mTOR inhibitor temsirolimus has shown to be clinical active in relapsed mantle cell lymphoma in a large multicenter phase III trial, which included patients with up to 7 prior lines of therapy. In this poor-risk population, the ORR was 22% using a regimen consisting of 175mg temsirolimus for 3 weeks given weekly, followed by 75mg/weekly or 25 mg/weekly until tumor progression or unacceptable toxicity occured. During the later therapy phase the average dose was 52 mg/week. The most prominent side effect in this trial was thrombocytopenia. PFS, which was the primary endpoint of this trial, was significantly superior using this regimen, in comparison to a standard treatment arm, which consisted of a variety of commonly accepted single agents [1]. Furthermore, a phase II trial by Smith and colleagues demonstrated single agent activity of temsirolimus in DLBCL and follicular lymphoma by achieving a ORR of 56% in relapsed patients. Especially a single agent activity of 28% in relapsed aggressive lymphoma is promising and merits further evaluation [2]. It seems therefore a logical consequence to incorporate temsirolimus into earlier treatment lines or to combine it with other therapies. Accordingly, a combination of temsirolimus with bendamustine and rituximab achieved a response in all patients evaluable with relapsed mantle cell and follicular lymphoma [3]. Of note, in recent in vitro experiments, additive action of temsirolimus, dexamethasone, cytarabine and platinum could be demonstrated [4]. Building on to this, the STORM trial combines temsirolimus with a well-established salvage treatment protocol (R-DHAP) with a known safety profile for the treatment of patients with refractory or relapsed DLBCL. The aim of this trial is to determine the safety, feasibility and clinical activity of the proposed regimen.

Methods:
The STORM study is a prospective phase I/II study to evaluate the safety, feasibility and activity of a salvage therapy consisting of the mTOR inhibitor temsirolimus added to standard therapy of rituximab and DHAP for the treatment of patients with relapsed or refractory DLBCL, the ClinicalTrials.gov Identifier is NCT01653067. The final protocol was jointly approved by the central ethics committee of this trial at the University of Heidelberg, Medical School (AFmu-017/2012, http://www.klinikum.uni-heidelberg.de) and by the ethics committees of all participating centres. This study complies with the Helsinki Declaration.
The STORM-trial consists of two phases. Phase I is a dose-escalation study of temsirolimus. The primary objective is to establish the maximum tolerated dose (MTD) of temsirolimus in combination with rituximab and DHAP. The secondary objective is to demonstrate that stem cells can be mobilized during this regimen in patients scheduled to proceed to high dose therapy. In phase II, the previously established maximum tolerated dose of temsirolimus will be used. The primary objective is to evaluate the overall response rate (ORR) in patients with relapsed DLBCL. The secondary objective is to evaluate progression free survival (PFS), overallsurvival (OS) and toxicity.
In phase I, the dose escalation phase of this trial, 6 patients will be included in each dose level. There will be four cohorts, administering up to a maximum of four cycles with 25 mg, 50 mg, 75mg or 100 mg temsirolimus on day 1 and 8 in combination with rituximab (375 mg/m2 day 2) and DHAP (dexamethasone 40 mg day 3–6, cisplatin 100 mg/m2 day 3, cytarabine 2 × 2 g/m2 day 4). Treatment is repeated on day 22 for up to a maximum of 4 cycles. After inclusion of six patients, each patient has to receive at least one complete cycle without experiencing any dose limiting toxicity, until the enrolment into the next cohort can be initiated. In phase II of the trial 40 patients will be included to receive the previously established full target dose. Special attention in phase I and phase II of the study is brought to monitoring of adverse events. Stem cell mobilization and subsequent high dose therapy and autologous stem cell transplantation can be performed in eligible patients. To be included into the STORM trial, patients must be at least 18 years old and have a histologically confirmed diagnosis of DLBCL according to the World Health Organization classification. There must be a documented relapse or progression after at least one prior treatment but a maximum of two prior treatments. Prior treatment must have included at least three cycles of anthracycline containing chemotherapy (e.g. CHOP-like). The histology has to be confirmed by a reference pathologist. Evaluation of CD20 status is compulsory. At least one measurable tumor mass (>1.5 cm x >1.0 cm), involvement of any organ or bone marrow infiltration must be present. In addition,adequate organ function and a Eastern Cooperative Oncology Group [ECOG] performance Status of lessthan 3 are essential for inclusion into the trial. Patients are required to use adequate contraception before entry and throughout the study, if appropriate. Naturally, patients 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.

Results:
Here we report on the preliminary results of part I of this clinical trial. 15 patients were included - 8 patients in the 25 mg cohort and 7 patients in the 50 mg cohort. Median age was 70 (49-76) years and median number of prior regimen was 1. Two DLTs (esophagus infection, venous thrombosis) were observed. The most frequent non-hematologic side effects were nausea (9 pts), epistaxis (7 pts), fatigue (6 pts), increased ALT (6 pts) and increased creatinine (6 pts). Frequent grade 3/4 events (n>2) in both cohorts (25mg|50mg) included leukopenia (6|5 pts - with a mean duration of 4.4 days | 6.7 days), thrombocytopenia (5|6pts - with a mean duration of 4.6 days | 11.9 days), lymphopenia (2|4pts), anemia (2|3pts), neutropenia (3|0pts), renal failure (2|1 pts) and infections (1|3 pts) (bladder infection, esophagus infection, central venous access infection, soft tissue infection, mucositis). For the part II proportion of the trial, a Temsirolimus dose of 25mg given on day 1 and 8 was defined as recommended dose. Evaluation for best response showed a response in 10/11 patients, with 2 CRs and one CRu. Four patients could not be evaluated for response at the time of this report. At a median follow-up of 6 months, 77% of evaluable patients are without signs of progression.

Conclusion:
Temsirolimus can be safely added to DHAP and Rituximab with promising activity. Recruitment into part II is ongoing.

STORM: Treatment algorithm



STORM Parameter PART I, patient characteristics

	total	25mg Torisel	50 mg Torisel
Parameter	N (15)	N(8)	N(7)
Age median; range	70 (49-76)	67 (54-76)	70 (49-75)
Sex f:m	6:9	3:5	3:4
prior treatments (median;range)	1 (1-2)	1(1-2)	1(1)

STORM Response PART I, preliminary results

End of treatment results

	Torisel 25mg n=8	Torisel 50 mg n=7
CR / CRu, n	1	2
partial response, n	5	2
progressive desease, n	0	1
Drop Out before assessment	2 (SAE renale failure; SAE allergic reaction)	2 (inclusion criteria fail; patient wish)
Patient without progression [at median Follow up of 6 Months]	6*	4
Patient with HD + auto. BSCT after STORM treatment	4	2

STORM Toxicities PART I, preliminary results

SAE CATEGORY	TERM	Patient ID	sex	age	time of occurrence
	Dental pain	0201	m	58	after c1
	Pain of the thoracical spine	0201			after c2
	Acute renal failure	0103	m	70	after c1
	Hyponatriemia	0103			after c1
SAR (DLT)	Thrombosis right V. jug. int.	0804	m	64	after c1
	Thrombosis left V. brachiocephalica	0804			after c1
	Acute renal failure	0804			after c2
	Nausea, renal failure	0206	m	63	in c2
	soft tissue infection	0908	f	76	after c2
	Elevation of CRP	0609	f	64	after c2
	Febrile neutropenia	0609			after c4
SAR (DLT)	Candida esophagitis	0711	m	70	in c1
SUSAR	Left ventricular systolic dysfunction	0711			after c1
SAR	Pneumonia	0912	m	62	after c1
	Pulmonary embolism	0912			after c1
	Acute renal failure	0912			after c2
	Pancytopenia	0912			after c2
SAR	Septicaemia	0713	f	71	after c4
SAR	Pneumonia	0713			after c4
SAR	Vomiting	0914	f	49	after c2
	Hearing loss	0914			in c2
SAR	Port infection	0715	m	72	after c2
SAR	Pancytopenia	0715			after c1

Dose limiting toxicities

Definition:	hematological	Any event not recovering to at least grade 2 after 28 days (exept Lymphopenia)
	non-hematological	Any grade III/ IV not recovering to grade II within 14 days

rated DLT`s

venous thrombosis	0804 - 25mg T, SAR, male, 64 years, after C1, resolved
esophagus infection	0711 - 50mg T, SAR, male, 70 years, in C1, resolved

Adverse Events

	TERM	25 mg Torisel, n	50mg Torisel, n
Most frequent AEs	Nausea	4	5
	Nose bleeding	6	1
	Fatigue	5	1
	Elevation ALT	4	2
	Elevation creatinine	5	1
AEs grade III/IV (n>2)	Leukopenia	6	5
	Thrombopenia	5	6
	Lymphopenia	2	4
	Anemia	2	3
	Neutropenia	3	0
	Renal Failure	2	1
	Infections	1	3

References:
1. Hess G et al, J Clin Oncol, 2009, 7(23):3822–3829.
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3. Hess G et al, Leukemia, 2015 Mar 13.
4. Zoellner A-K, et al, Onkologie 2011, 34(6).

Competing interests: The trial is funded by Pfizer Inc., New York, USA. Funding includes trial organization and monitoring by the IZKS Mainz, the statistical analysis, data management and the supply of the study medication.