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The mTOR Inhibitor Temsirolimus Added to Rituximab Combined With Dexamethasone, Cytarabine, and Cisplatinum (R-DHAP) for the Treatment of Patients With Relapsed or Refractory DLBCL – Results From the Phase-II STORM Trial

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Abstract

There is a high need for novel treatment options in relapsed and refractory diffuse large B-cell lymphoma. Single agent mammalian target of rapamycin (mTOR) inhibitor treatment has shown promising efficacy in this entity. Here, we report on the results of the mTOR-inhibitor temsirolimus combined to standard rituximab-DHAP salvage regimen in a prospective, multicenter, phase II, open-label study. The STORM regimen consisted of rituximab 375 mg/m^2 (day 2) and DHAP (dexamethasone 40 mg day 3-6, cisplatinum 100 mg/m^2 day 3, cytarabine 2 × 2 g/m^2 day 4) with temsirolimus added on day 1 and 8 of a 21-day cycle, with 2 to 4 cycles planned. In part I, dose levels of 25, 50, 75, and 100 mg for temsirolimus were predefined. Based on the observed toxicity profile, a temsirolimus dose of 25 mg was defined as recommended dose for the part II extension cohort of the trial. The intention-to-treat cohort comprised 53 patients. Median age was 63 years and median number of prior regimen was 1. All but 1 patient had prior rituximab exposure. Temsirolimus dose was 50 mg on day 1 and 8 in 6 patients from the part I of the trial and 25 mg in the remaining 47 patients. In general, treatment was well tolerated with leucopenia and thrombocytopenia as most frequent severe adverse events. The overall response rate after the last cycle of temsirolimus R-DHAP was 66% with 24% complete responses. The ability to mobilize stem cells was not impaired by the treatment regimen. Twenty-eight patients received consolidation treatment with high-dose therapy (HDT) and stem cell transplantation. Median duration of response was not reached. The total 2-year progression-free survival (PFS) and overall survival (OS) were 53% and 59%. Patients who were consolidated with HDT achieved a 2-year PFS and a 2-year OS of 77.8% and 82.1%, respectively. We conclude that temsirolimus can be safely added to rituximab and DHAP with promising activity.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma in the Western hemisphere.[1,2] Despite improvement of first-line therapy with the advent of rituximab and risk adapted treatment strategies,[3–5] a large proportion of patients will ultimately succumb to relapsed and refractory (r/r) disease. The current standard treatment of r/r DLBCL primarily consists of a intensified salvage therapy preceding transplant strategies, with regimens like R-DHAP, R-ICE, or R-GDP widely accepted.[6,7] However, these regimens frequently fail to induce sufficient responses to allow for consolidation treatments. Therefore, there is an ultimate need for improved salvage treatment approaches for r/r DLBCL. The mammalian target of rapamycin (mTOR) kinase is a key component of the PI3K/Akt pathway and involved in the transduction of downstream signals. This results in activation of nuclear transcription factors in healthy and malignant

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cells. In lymphoma, a variety of mechanisms have been identified, which disturb the normal function of mTOR, for example, loss of the negative regulator PTEN, overexpression of mTOR, or overexpression of target genes as c-MYC and cyclin D1.[8,9] Temsirolimus is a selective inhibitor of mTOR. Besides solid cancers temsirolimus was evaluated in a variety of lymphoma entities.[10] In r/r DLBCL, the response rate was 28% as single agent,[11] stimulating further development. As preclinical data have shown synergism between mTOR inhibitors and cytotoxic agents,[12] we postulated that the combination of mTOR inhibition to chemotherapy results in improved efficacy with acceptable toxicity. Consequently, in this study, we combined temsirolimus to the standard regimen R-DHAP (rituximab, dexamethasone, cytarabinoside, cisplatinum) for the treatment of r/r DLBCL.[13]

Methods

Conduct of the trial

According to national regulations, the study was approved by the competent authority Federal Institute for Drugs and Medical Devices (BfArM) and received a favorable opinion in a harmonized approach of the appropriate Ethic's Committees. It was conducted in accordance with the German Medicines Act and Good Clinical Practice guidelines. Patients were required to sign informed consent before any study-related procedures. Trial conduct was supported by the Interdisciplinary Center for Clinical Trials (IZKS) of the University Medical Center Mainz. The trial was registered on EudraCT (2011-001491-20) and ClinicalTrials.gov (NCT01653067).

Study design

This was a prospective multicenter, phase II, open-label study to evaluate a salvage regimen of the mTOR inhibitor temsirolimus (Torisel) added to the standard therapy of rituximab and DHAP. The STORM-trial consisted of 2 parts. In the part I (dose escalation of temsirolimus), the primary objective was to establish a maximum tolerated dose of temsirolimus in combination with rituximab and DHAP. In the part II (full target dose), the primary objective was to evaluate the overall response rate (ORR). It was planned that at least 40 patients were enrolled to demonstrate an ORR of 65% with a complete response (CR) of 40%. The recruitment period lasted from April 2013 to August 2016.

Main eligibility criteria

Adult patients (≥18 years) with r/r DLBCL were eligible after signing informed consent. Patients had to have a histologically proven diagnosis of DLBCL according to the World Health Organization (WHO) classification, refractory disease, relapse, or progression following at least 1 treatment but a maximum of 2 prior lines. Since at the time the study was planned cell of origin (COO) status was not mandatory based on the WHO classification COO analysis was not routinely performed. Prior treatment must have included at least 3 cycles of anthracycline containing chemotherapy (eg, CHOP-like) including an anti-CD20 antibody. There had to be at least 1 measurable tumor mass (>1.5 cm × >1.0 cm).

Participants had to have an adequate bone marrow reserve (platelets of at least 75000/μL, absolute neutrophil count at least 1500/μL, hemoglobin of at least 10 g/dL) as well as liver (alanine aminotransferase < 2.5 × upper limit of normal [ULN]; aspartate aminotransferase < 2.5 × ULN, total bilirubin < 1.5 × ULN except chronic hepatic conditions leading to bilirubin increase but not interfering therapy, eg, Gilbert's Syndrome) and renal function (calculated creatinine clearance >70 mL/min). Eastern Cooperative Oncology Group (ECOG) performance status had to be <3. If applicable, effective birth control was to be used.

Treatment regimen

In part I of the trial, patients were planned to receive 25, 50, 75, or 100 mg of temsirolimus on day 1 and day 8 in combination with R-DHAP (rituximab 375 mg/m^2 day 2, dexamethasone 40 mg day 3-6, cisplatinum 100 mg/m^2 day 3, cytarabine 2 × 2 g/m^2 day 4, q 22 days) in sequential cohorts. Cisplatinum could be replaced in the consecutive cycles by carboplatinum AUC 5 if the patient experienced kidney toxicity in the previous cycle, that is, decrease of creatinine clearance to 60 mL/min or lower. Two cycles of temsirolimus and R-DHAP were scheduled before first restaging, if clinically indicated, for example, to deepen response, patients were allowed to receive 2 further cycles of the regimen. Stem cell mobilization and subsequent high-dose consolidation therapy (HDCT) and autologous stem cell transplantation could be performed based on investigators description. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Dose-limiting toxicities were defined as any CTCAE grade V toxicity with an at least possible relationship to the trial treatment and 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). Granulocyte colony-stimulating factor use was allowed up to the investigator discretion. In addition, any nonhematological 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 was considered as dose-limiting toxicity (DLT). Lymphopenia was not considered as DLT. For maximum tolerated dose determination, a 6 + 6 standardized design was chosen. It was planned to include 6 patients into each dose level. After inclusion of 6 patients, each patient had to receive at least 1 complete cycle without DLT until the enrolment into the next cohort could be initiated. DLTs were discussed with the Data Safety Monitoring Board (DSMB) for further recommendations.

Evaluations

All primary and secondary analyses were performed for the intention to treat (ITT) population which comprised all patients who received at least 1 dose of study treatment. As at the time of study initiation, there was limited access to PET-scanning, response to treatment was defined according to the International Response Criteria for Non-Hodgkin Lymphoma.[14] Initial staging included computed tomographic scans of the neck, chest, abdomen, and pelvis and radiological evaluation of all the affected regions. Restaging was scheduled after 2 cycles and at the end of treatment after final dose. Additional CT was performed every 3 months in the first year, every 6 months in the second and third year, and every 12 months after the third year of follow-up. Patients were followed up to 5 years after end of the last STORM cycle. Progression-free survival (PFS) was defined as time from treatment start to date of relapse, disease progression or death, or was censored at the last tumor evaluation date in case of no event; overall survival (OS) was measured as time from first dose to date of death or was censored at the last follow-up. After progression or the initiation of a new therapy, patients were followed with respect to survival. Duration of response (DoR) was defined as time from initial response to progression of disease or was censored in case of death or at the last tumor evaluation date in case of no event.

Statistical analysis

Primary objectives

In the phase I proportion of the trial occurrence of DLTs were monitored to determine the maximum tolerated dose of temsirolimus. In the phase II proportion of the trial, the primary analysis comprised ORR after the last cycle of temsirolimus R-DHAP. Overall response was defined as complete response (CR or CRu [CR unconfirmed]) or partial response at the respective time point based on International Working Group (IWG) recommendations. For overall response assessments until the end of follow-up, the last observation carried forward method was applied in case of missing values at the respective time point. 95% confidence intervals were given.

Secondary objectives

PFS, OS, and DoR at end of last follow-up were analyzed for the combined data of part I and part II of the trial. Results for time to event end points were calculated according to Kaplan-Meier estimator. The number of successful transplantations after stem cell mobilization and subsequent HDCT was analyzed descriptively.

Safety analysis

Special attention in part I and part II of the study was brought to monitoring of adverse events. Adverse events were classified by system organ class (SOC) 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. SAS Version 9.4 was used for all calculations.

Results

Patients

In total, 55 patients were assessed for eligibility. Fifty-three patients were enrolled, 15 patients in part I and 38 in part II of the study. Two patients were excluded from the study: 1 patient was identified as screening failure and another patient withdrew informed consent before start of treatment, respectively. Patient characteristics are shown in Table 1. In brief, the ITT population comprised 53 patients. Thirty-three patients (62%) were male, median age of the study population was 63 years (Q1-Q3: 54-67 years). Fifty patients had received 1 prior treatment regimen. All but 1 patient was pretreated with rituximab. Median time to relapse from initial lymphoma therapy to study enrolment was 10 months and mean time was 24.2 months (range 2-183 months). The last treatment of the last patient was in October 2016 and last follow-up took place in October 2018. Three patients were not available for efficacy analysis. Of these, 2 patients withdrew consent prior and 1 patient died before first disease evaluation to restaging. The CONSORT diagram of the trial is shown in Figure 1.

Table 1.

Patient Characteristics

Variable	50 mg (N = 6)	25 mg (N = 47)	Total (N = 53)
Age (y), median (range)	68 (50–73)	61 (23–77)	63 (23–77)
Age >60 y, n (%)	5 (83)	24 (51)	29 (55)
Sex, n (%)			
Male	3 (50)	30 (64)	33 (62)
Female	3 (50)	17 (36)	20 (38)
Stage at inclusion (%)			
I	0 (0)	2 (4)	2 (4)
II	0 (0)	17 (36)	17 (32)
III	5 (83)	9 (19)	14 (26)
IV	1 (17)	19 (40)	20 (38)
ECOG performance status, n (%), missing: 2			
0	5 (83)	27 (60)	32 (63)
1	1 (17)	12 (27)	13 (25)
2	0 (0)	6 (13)	6 (12)
IPI score, n (%), missing: 26			
1	0 (0)	3 (14)	3 (11)
2	1 (20)	5 (23)	6 (22)
3	3 (60)	10 (45)	13 (48)
4	1 (20)	3 (14)	4 (15)
5	0 (0)	1 (5)	1 (4)
Baseline aaIPI-score, n (%), missing: 29			
0	0 (0)	1 (4)	1 (4)
1	0 (0)	9 (39)	9 (38)
2	1 (100)	10 (43)	11 (46)
3	0 (0)	3 (13)	3 (13)
Disease stage III/IV, n (%), missing: 19	6 (100)	28 (60)	34 (64)
Bulky disease (>7.5 cm), n (%)	0 (0)	16 (34)	16 (30)
Elevated LDH, missing: 20	0 (0)	17 (54)	17 (51)
Bone marrow involvement, missing: 9	0 (0)	5 (13%)	5 (11)
Number of prior regimens (median, range: 1; 1–2) (%)			
1	5 (83)	45 (96)	50 (94)
2	1 (17)	2 (4)	3 (6)
≥3	0 (0)	0 (0)	0 (0)
Prior radiotherapy	0 (0)	13 (28)	13 (25)
Prior rituximab	6 (100)	46 (98)	52 (98)
Time interval since last treatment <1 y	4 (67)	32 (68)	36 (68)
Response to most recent prior therapy, missing: 2 (%)			
Complete response	5 (83)	20 (44)	25 (49)
Partial response	0 (0)	9 (20)	9 (18)
Stable disease	0 (0)	3 (7)	3 (6)
Disease progression	1 (17)	13 (29)	14 (27)

aaIPI-score = age-adjusted international prognostic index; ECOG = Eastern Cooperative Oncology Group; IPI = international prognostic index; LDH = lactate dehydrogenase.

Completion of treatment and relative dose intensity

In part I of the study, 9 patients received a dose of 25 mg temsirolimus and 6 patients received a dose of 50 mg temsirolimus on day 1 and day 8 in combination with R-DHAP per treatment administration. In part II of the study, 38 patients received the recommended phase II dose of 25 mg temsirolimus on day 1 and day 8 as determined in part I of the study. Median treatment duration measured from first day to last day of treatment was 51.6 days. Overall, 83% of patients completed at least 2 treatment cycles (median number of completed cycles: 2, range: 0-4 cycles; Table 1). Median time between cycle 1 and 2 was 16 days, between cycle 2 and 3 as well as cycle 3 and 4 the median time was 20 days. Thirty-one patients received cisplatin only (9 in part I and 22 in part II), 21 patients received both cisplatin and carboplatin (6 in part I and 15 in part II), and 1 patient received carboplatin only in part II. Dose adherence was high (Table 2).

Maximum tolerated dose

Two formal dose-limiting toxicities were observed; 1 esophagus infection in the 50 mg cohort and 1 venous thrombosis in the 25 mg cohort. Additionally, in 3 of 6 patients of the 50 mg cohort, a NCI CTCAE grade IV thrombocytopenia occurred. In 2 of these patients, the NCI CTCAE grade IV thrombocytopenia resolved only after 43 days. After discussion with the data safety monitoring board therefore the recommended dose of temsirolimus was determined as of 25 mg on day 1 and 8, which was then used for the phase II proportion of the trial.

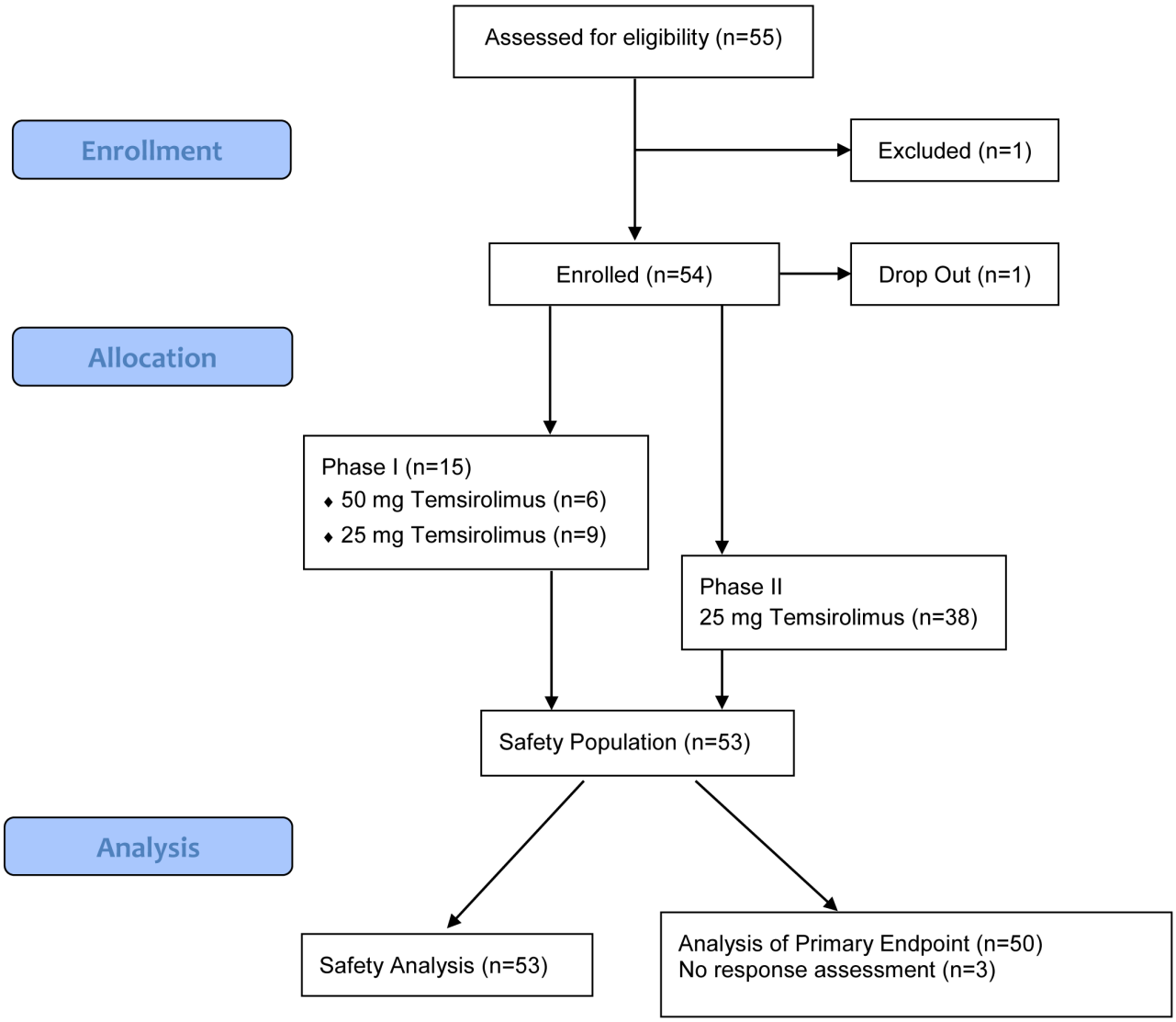

Figure 1. CONSORT chart.

Number of successful stem cell mobilizations und transplantations

Stem cells mobilization was initiated in 40 patients (78%) of which 38 patients (95%) had a successful mobilization. Of the 38 patients who successfully collected stem cells, 23 received an autologous stem cell transplantation (SCT). Furthermore, 5 patients received an allogeneic SCT based on the investigator discretion. Of the patients who received a transplant, 14 patients had an early relapse after the last lymphoma therapy.

Adverse events

Overall, treatment was well tolerated. A total of 1678 adverse events (AEs) were reported (32 per patient). Interestingly, a trend of a dose-dependent difference of AE-number was noted, as 253 AEs (15%, 42 per patient) occurred in the group of patients treated with 50 mg temsirolimus and 1425 AEs (85%, 30 per patient) occurred in the group of patients treated with 25 mg temsirolimus. Supplemental Digital Content 1, Table 1S, http://links.lww.com/HS/A200 shows the summary of related AEs allocated to MedDRA SOCs and treatment group. Overall, 538 AEs (32%) were graded as severe (CTCAE grade >2). Again, there was a trend to higher rate of severe AE with higher doses of temsiroliums with 99 (18%, 17 per patient) of the 538 severe AEs occurring in the group of patients treated with 50 mg temsirolimus and 439 (82%, 9 per patient) in the group of patients treated with 25 mg temsirolimus. The most

Table 2.

Treatment

Number of Started Treatment Cycles	50 mg (N = 6) (%)	25 mg (N = 47) (%)	Total (N = 53) (%)
1	1 (17)	5 (11)	6 (11)
2	0 (0)	15 (32)	15 (28)
3	1 (17)	20 (43)	21 (40)
4	4 (67)	7 (15)	11 (21)
Applications in Relation to Total Number of Cycles Started = 143 (%)			
Temirolimus	275/286 (96)		
Rituximab	143/143 (100)		
Cisplatinum/carboplatinum	143/143 (100)		
Cytarabine	142/143 (99)		
Dexamethasone	545/572 (95)		

frequent severe AE (>10%) are shown in Table 3 and were leukopenia (75%), thrombocytopenia (83%), anemia (57%), hypokalemia (25%), 102 serious adverse events (SAEs) (6%, 2 per patient) were reported. Sixty-five SAEs were judged as related to the study medication and were considered as serious adverse reactions (SARs). Nine (14%, 2 per patient) of SARs occurred in the group of patients treated with 50 mg temsirolimus and 56 (86%, 1 per patient) occurred in the group of patients treated with 25 mg temsirolimus. Three 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. The most frequent SAEs (>5%) were febrile neutropenia (7 patients) and thrombocytopenia (5 patients).

Response

The ORR in the ITT population at the end of the salvage therapy with temsirolimus R-DHAP was 66% (33 patients) with a 95% confidence interval of 52.87%-79.13%. CR was achieved by 24% (12 patients), of which 1 patient had an unconfirmed CR. Three patients had no response assessment and were excluded from the primary analysis. At end of last follow-up (ie, the last tumor evaluation after end of the last STORM-cycle), the ORR was 72% (36 patients) with a 95% confidence interval of 59.55%-84.45% and the CR rate was 42% (28.32-55.68). Patients who received a SCT achieved an ORR of 93% (26 of 28 patients) after transplantation while patients without SCT had an ORR of only 45%. CR rates were 61% (17 patients) in patients with SCT versus 18% (4 patients) without HDCT. Patients with HDCT who received an autologous stem cell transplantation had an ORR of 91% (21 patients) and a CR rate of 65% (15 patients). Mean DoR was not reached.

Table 3.

Related Adverse Events With a Frequency >10% of Patients

System Organ Class	Preferred Term	N	%
Blood and lymphatic system disorders	Anemia	30	57
	Febrile neutropenia	7	13
	Leukopenia	40	75
	Lymphopenia	11	21
	Neutropenia	24	45
	Thrombocytopenia	44	83
Gastrointestinal disorders	Constipation	9	17
	Diarrhea	18	34
	Nausea	30	57
	Vomiting	16	30
General disorders	Asthenia	6	11
	Fatigue	22	42
	Mucosal inflammation	14	26
	Pyrexia	13	25
Investigations	Alanine aminotransferase increased	6	11
	Blood cholesterol increased	7	13
	Weight decreased	10	19
Metabolism and nutrition disorders	Decreased appetite	12	23
	Hypertriglyceridemia	6	11
	Hypokalemia	13	25
Nervous system disorders	Dizziness	7	13
	Dysgeusia	9	17
	Headache	11	21
	Polyneuropathy	6	11
Respiratory, thoracic, and mediastinal disorders	Epistaxis	9	36

Survival

Two-year PFS rate was 53.1% for the entire group. Rates differed significantly between patients with and patients without HDCT therapy, with 2-year PFS rates of 77.8% and 24.0%, respectively. When separated by autologous versus allogeneic stem cell transplantation, 2-year PFS was 95.5% versus 0%. For OS, the 2-year survival rate was 58.9% for the entire group. Separated by HDCT, a 2-year OS rate of 82.1% in the group with and an OS rate of 30.6% in the group without HDCT were observed. When separated by autologous versus allogeneic stem cell transplantation, 2-year OS was 95.7% versus 20%. Patients with late relapse had a superior PFS compared to patients with early relapse. Efficacy data are shown in Table 4 and in Figures 2–4 and Supplemental Digital Content, Table S1, http://links.lww.com/HS/A199.

Discussion

The current standard treatment of patients r/r DLBCL consists of an intensified salvage immunochemotherapy and, in case of chemosensitive disease, consolidation high-dose therapy (HDT) with either autologous or, in selected cases, allogeneic transplantation.[15] However, in the rituximab era, HDT and autologous transplantation have shown only limited benefit in r/r DLBCL and allogeneic transplantation is limited to a particular patient population. This is underlined by the results of the CORAL trial, which showed that patients with r/r DLBCL experiencing relapse after today's standard rituximab containing primary treatment have an adverse prognosis with standard salvage strategies, especially if relapse occurs within the first year after therapy or if the disease is primarily refractory.[6] Therefore, there is an ultimate need for improved salvage treatment approaches for r/r DLBCL.

As mTOR inhibitors have shown preliminary efficacy in this entity as single agent,[11] in the STORM trial, we aimed to evaluate the addition of the mTOR inhibitor temsirolimus to the standard rituximab-DHAP regimen. In the dose escalation in part I of the trial, temsirolimus 50 mg on day 1 and 8 resulted in pronounced and prolonged thrombocytopenia interfering with treatment continuation. Therefore, temsirolimus at a dose of 25 mg on day 1 and 8 was selected as recommended dose for the subsequent phase II part of the trial. Consequently, the observed toxicity of the combination of standard rituximab DHAP and temsirolimus 25 mg on day 1 and 8 was within expected limits

Table 4.

Response Rates, Progression-free, and Overall Survival

Overall Response	50 mg (N = 6) (%)	25 mg (N = 47) (%)	Total (N = 53)
At end of salvage therapy, missing = 3			
CR	2 (40)	10 (22)	12 (24%)
PR	2 (40)	19 (42)	21 (42%)
CR + PR	4 (80)	29 (64)	33 (66%)
SD	0 (0)	7 (16)	7 (14%)
PD	1 (20)	9 (20)	10 (20%)
At end of follow-up missing = 3			
CR	4 (80)	17 (38)	21 (42%)
PR	0 (0)	15 (33)	15 (30%)
CR + PR	4 (80)	32 (71)	36 (72%)
SD	0 (0)	2 (4)	2 (4%)
PD	1 (20)	11 (24)	12 (24%)
Progression-free survival at 24 mo			53%
Overall survival at 24 mo			59%

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

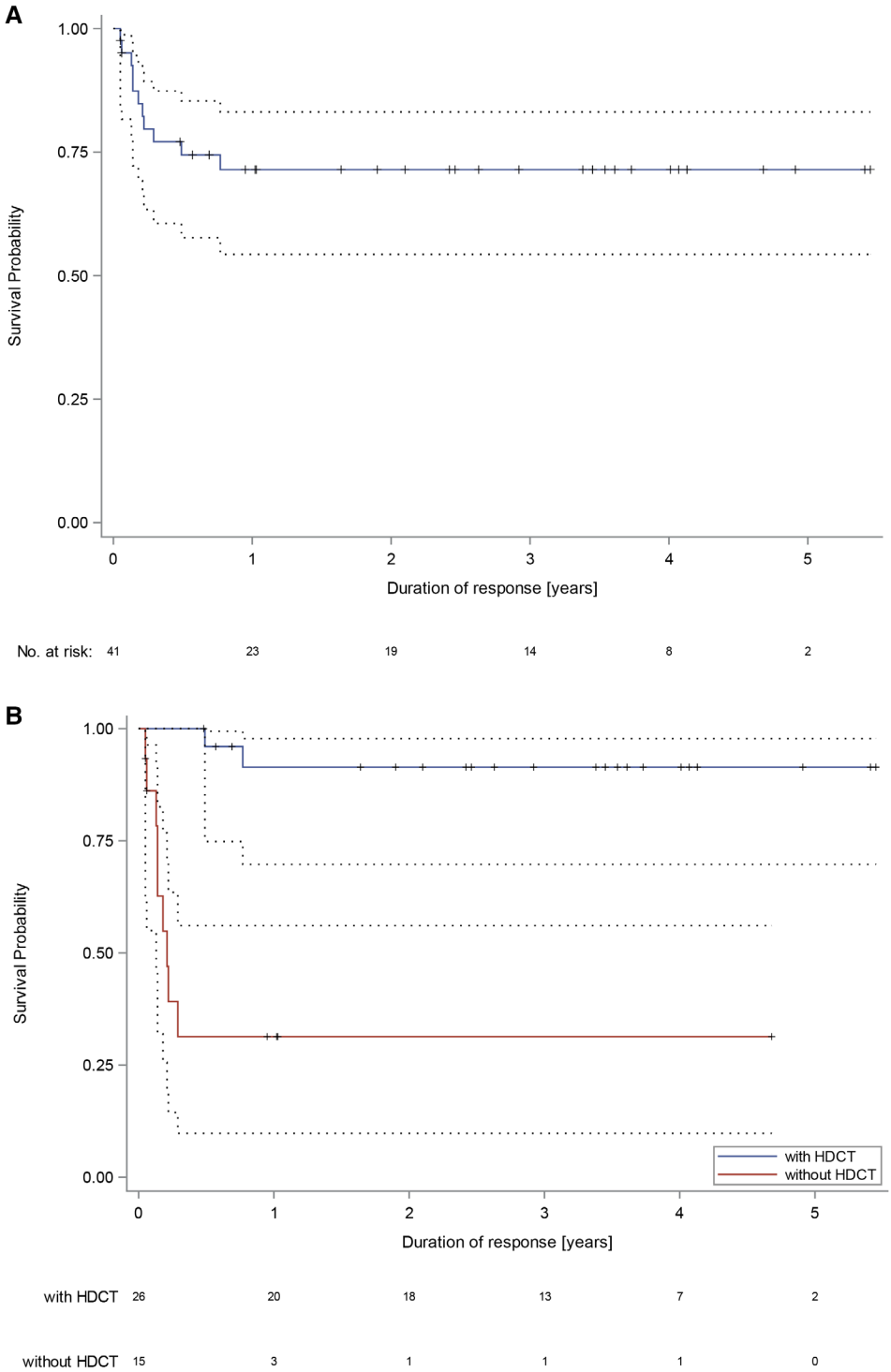

Figure 2. Duration of response. Kaplan-Meier analysis of duration of response (A) in the ITT population (B) related to HDCT and subsequent stem cell transplantation. Dotted lines represent 95% confidence intervals. HDCT = high-dose consolidation therapy; ITT = intention to treat.

during the trial with neutropenia and thrombocytopenia as most frequent SAEs.

After the last cycle of temsirolimus R-DHAP, we observed an ORR of 66% with 24% complete remissions. This is a remarkable result, in particular in the light of rituximab-pretreated patient population. If PET-CT would have been used, in particular, CR rates might have been superior in contrast to conventional CT scanning.[16] Not surprisingly, response rates could be further improved after HDT and stem cell transplantation in eligible patients.

The observed response rate of 66% (24% CR) and a 2-year PFS of 51% in the STORM trial compares favorably to previous trials that have evaluated standard R-DHAP, R-ICE, R-GDP, or ofatumumab DHAP after prior rituximab exposure. In the CORAL trial, where R-DHAP or R-ICE were investigated, patients with prior rituximab treatment achieved an ORR of 51% and a 3-year PFS of 21%.[6] Crump et al[7] compared R-DHAP and R-GDP in r/r DLBCL and observed an ORR of 45.1% in the GDP group and 44.1% in the DHAP group and an event free 4-year survival of 26% in both groups. The

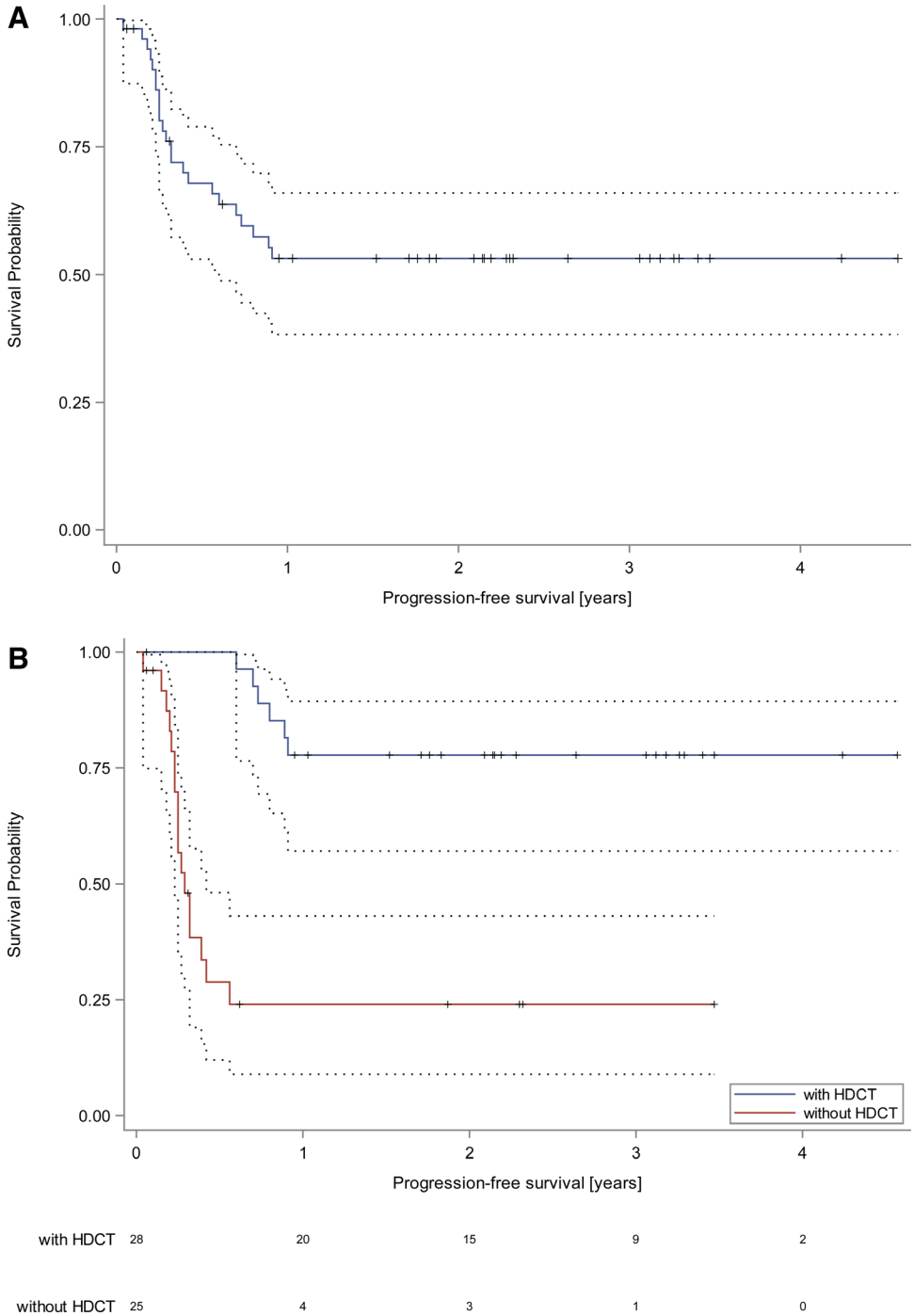

Figure 3. Progression free survival. Kaplan-Meier analysis of progression-free survival (A) in the ITT population (B) related to HDCT and subsequent stem cell transplantation. Dotted lines represent 95% confidence intervals. HDCT = high-dose consolidation therapy; ITT = intention to treat.

ORCHARD trial examined R-DHAP and ofatumumab DHAP in r/r DLBCL and found an ORR of 38% after ofatumumab DHAP and 42% after R-DHAP with a 2-year PFS of 24% and 26% only, respectively. Of note, in the ORCHARD trial, only 151 of 447 patients actually got to autologous SCT. Of these patients, 99 of 151 were PET–ve after salvage pre-ASCT, while the respective 2-year PFS rates in PET–ve and PET+ve patients were 73% and 32%.[17]

Recently the treatment options in r/r DLBCL have significantly expanded with the introduction of antibody drug conjugates such as polatuzumab,[18] bispecific antibodies,[19,20] and in particular CAR T-cell treatment.[21,22] However, definite proof of superiority still needs to be shown in confirmatory trials. Until the results of these trials are available, salvage immunochemotherapy and consolidation with HDT in chemosensitive eligible patients remains the international therapeutic standard in r/r DLBCL.[15] Interestingly, in trials examining CAR T-cell treatment in r/r DLBCL, it was observed that this treatment is particularly feasible with few cytokine release syndromes and little neurotoxicity in patients with a low tumor volume,[21,22] underlining that there still is a need for effective salvage regimens even in the CAR T-cell era. In addition, beside direct inhibition of

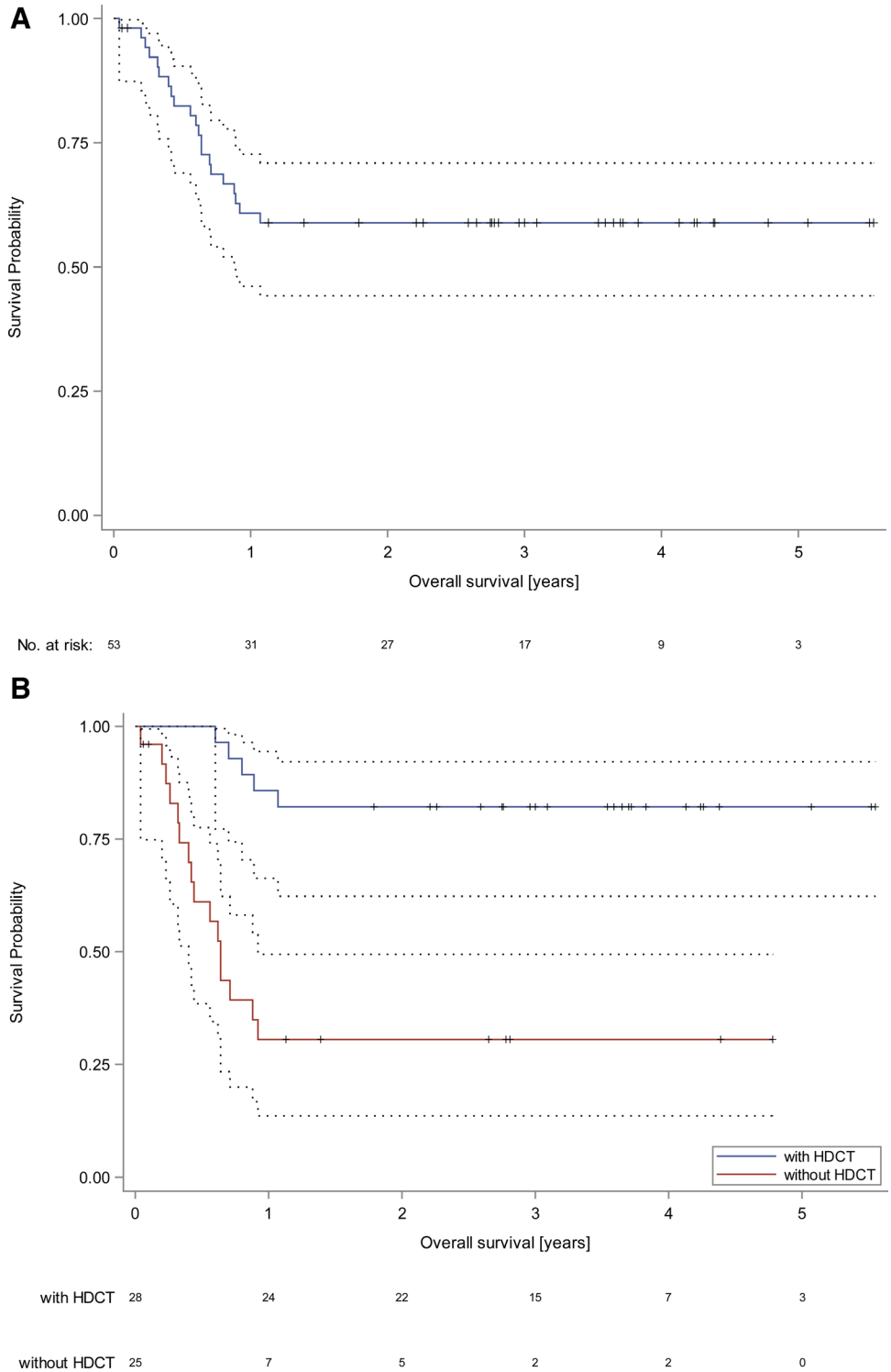

Figure 4. Overall survival. Kaplan-Meier analysis of overall survival (A) in the ITT population (B) related to HDCT and subsequent stem cell transplantation. Dotted lines represent 95% confidence intervals. HDCT = high-dose consolidation therapy; ITT = intention to treat.

mTOR by temsirolimus, upstream blockade of mTOR signaling with PI3 kinase inhibitors might further improve tumor control in DLBCL.[23]

Taken together, we conclude that temsirolimus can be safely added to Rituximab and DHAP with promising activity. However, there are several important limitations to our results. First, as PET was not performed in the majority of patients, we could not determine treatment response according to the revised IWG criteria,[16] which today is the international gold standard. Second, COO and high-risk molecular characteristics (eg, double hit, triple hit) were not assessed at the time of relapse, therefore we cannot address the respective subgroups in our analysis. Finally, our results are based on a limited number of patients but underline a potential role of mTOR inhibitors as additive to chemoimmunotherapy in aggressive lymphoma. Everolimus combined with R-CHOP results induced a high complete

metabolic remission rate (96%) in a small phase-II trial of 24 patients with DLBCL.[24] While postinduction maintenance treatment with everolimus after R-CHOP failed to improve the PFS in a randomized phase-III trial,[25] this is more likely attributed to the questionable concept of maintenance in DLBCL as to the question if a synergism can be observed if mTOR inhibitors are combined with chemotherapy. In conclusion, the promising results of our trial merits further development in prospective comparisons for salvage therapies in r/r DLBCL.

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