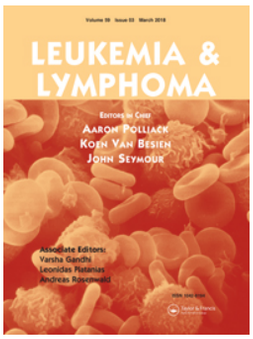

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Comparison of two doses of intravenous temsirolimus in patients with relapsed/refractory mantle cell lymphoma

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ABSTRACT

Temsirolimus 175 mg once-weekly for 3 weeks, followed by 75 mg once-weekly intravenously dosed (175/75 mg) is approved in the European Union for treatment of relapsed/refractory mantle cell lymphoma (MCL). A phase IV study explored whether similar efficacy, but improved safety could be achieved with 75 mg without 175 mg loading doses (ClinicaTrials.gov: NCT01180049). Patients with relapsed/refractory MCL were randomized to once-weekly temsirolimus 175/75 mg ($n = 47$) or 75 mg ($n = 42$). Treatment continued until objective disease progression. Primary endpoint: progression-free survival (PFS). Secondary endpoints included overall survival (OS) and adverse events (AEs). Median PFS was 4.3 versus 4.5 months (hazard ratio [HR] 0.731; 80% confidence interval [CI], 0.520–1.027), and median OS 18.7 versus 11.0 months (HR 0.681; 80% CI, 0.472–0.982) with 175/75 mg versus 75 mg. There were fewer patients with serious AEs, dose reduction, or death with 175/75 mg (57.4%, 48.9%, and 48.9%) versus 75 mg (73.8%, 64.3%, and 65.1%). Temsirolimus 175/75 mg remains the preferred dosing regimen for relapsed/refractory MCL.

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Temsirolimus; mantle cell lymphoma; progression-free survival; overall survival; safety

Introduction

Mantle cell lymphoma (MCL) is a relatively rare subtype of non-Hodgkin lymphoma, diagnosed in ~6–8% of all cases, predominantly in males aged >60 years [1–3]. MCL usually has an aggressive clinical course: although a growth pattern resembles low-grade lymphoma, it develops resistance to conventional chemotherapy relatively early and is considered incurable with conventional chemotherapy [1,4]. The majority of individuals have intermediate-high-risk or high-risk disease; ~60–70% of patients with MCL have advanced disease (Ann Arbor stage IV) at the time of initial diagnosis [5–7].

Temsirolimus, a selective inhibitor of mTOR, is approved in the European Union for the treatment of adult patients with relapsed and/or refractory MCL at an intravenous loading dose of 175 mg once-weekly for the first 3 weeks followed by 75 mg intravenously once-weekly (temsirolimus 175/75 mg) [8]. This approval was based on an overall positive benefit-risk assessment demonstrated in the pivotal phase III study where temsirolimus 175/75 mg prolonged progression-free survival (PFS) significantly over investigator's choice (median: 4.8 versus 1.9 months; hazard ratio [HR] 0.44; 97.5% confidence interval [CI], 0.25–0.78; $p = .0009$) [8].

Despite the improvement in PFS versus investigator's choice, the 175/75-mg dose regimen was associated with higher incidence of grade ≥3 adverse events (AEs) and serious AEs relative to investigator's choice [8]. However, as the initial loading dose had been selected based on individual tolerability rather than on a precise pharmacokinetic modeling, it was questioned whether this intensive and potentially more toxic treatment phase is required or could be skipped, thereby improving tolerability without compromising efficacy. To this intent, a phase IV study was conducted to explore whether similar efficacy but improved safety could be achieved with an alternative temsirolimus dosing regimen that removes the first three loading doses of temsirolimus 175 mg in the treatment of patients with relapsed/refractory MCL.

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Methods

Patients

Key inclusion criteria included age ≥18 years, histologically confirmed refractory and/or relapsed MCL, immunophenotype, and cyclin D1 analysis after receiving 2–7 prior therapies. Prior treatment must have included an alkylating agent and an anthracycline and rituximab, individually or in combination, and could have included hematopoietic stem cell transplant, i.e. induction plus consolidation plus maintenance. Patients had to have measurable disease, Eastern Cooperative Oncology Group performance status 0–2, and adequate organ and marrow function. Key exclusion criteria included having active central nervous system metastases (except for clinically stable brain metastases), and any prior history of noninfectious interstitial pneumonitis/interstitial lung disease. Patients were also excluded if they received any of the following treatments: chemotherapy, radiotherapy, immunotherapy, or major surgery ≤3 weeks prior.

Study design

This was a phase IV, multicenter, randomized, open-label study of temsirolimus in patients with relapsed, refractory MCL (ClinicaTrials.gov: NCT01180049). The study was conducted in 16 countries: Australia, Belgium, Bulgaria, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Netherlands, Poland, Republic of Korea, Romania, Russian Federation, Serbia, and USA. The first patient was enrolled on 10 March 2011.

The study protocol, amendments, and informed consent forms were reviewed and approved by the institutional review board or independent ethics committee at each study center. The study was conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws. Informed consent was obtained from each patient prior to study initiation.

Procedures

In this study, previously heavily treated (2–7 lines of prior therapy) patients with relapsed/refractory MCL were stratified by the histologic subtype (blastoid versus nonblastoid versus unknown histology) and randomized (1:1) to receive intravenous temsirolimus 175/75 mg or 75 mg weekly. Due to limited sample size and the expectation of strata sizes being significantly disproportioned, the primary analysis was not stratified. Treatment continued until objective disease progression according to Cheson Criteria (version 1999) [9], provided patients were tolerating treatment. Temsirolimus dose reductions to 75 mg (in the 175/75-mg group), 50 mg, 25 mg, and 15 mg were permitted on the basis of individual tolerability. Patients withdrawn from the study were not replaced, irrespective of the reason for withdrawal.

The study included a 4-week screening phase, a treatment phase, and a long-term follow-up phase. 'On-treatment' was defined as the time from the first dose until 30 days after the last dose of temsirolimus. 'On-study' ranged from the time of randomization until patient was reported off-study due to death, withdrawal of consent, or lost to follow-up. An external data monitoring committee (EDMC) was responsible for routine monitoring of the safety of patients in the study according to the EDMC Charter.

Assessments

Efficacy was assessed using the modified International Working Group response criteria (Cheson Criteria, version 1999), which were standard at the time of study initiation [9]. Objective tumor responses were determined by computed tomography scans, as well as clinical information, including B-symptom evaluation, physical examination, Eastern Cooperative Oncology Group performance status, assessment of liver and spleen, laboratory assessments such as bone marrow biopsies and/or aspirates, biochemical markers of disease activity (i.e. lactate dehydrogenase [LDH]), and hematology results.

Safety assessment included AEs classified by type, incidence, severity, seriousness, relationship to the study drug, and laboratory abnormalities (severity graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). Any serious AEs beyond 30 days after the last dose of study drug considered at least possibly treatment-related were reported. AEs of interest (infection- and bleeding-related) were also assessed on an ongoing basis while on study treatment. Other safety assessments included physical examination and vital signs, 12-lead electrocardiogram, and laboratory test evaluations. Survival follow-up was conducted every three months from the time of the last temsirolimus infusion until death or withdrawal of informed consent.

Statistical analyses

Sample size was based on clinical considerations. The primary endpoint was PFS (by an independent

assessor), defined as the time from randomization to progressive disease or death, censored at the last adequate tumor assessment prior to initiation of new anticancer therapy. Secondary endpoints included overall survival (OS), objective response rate (ORR), Investigator-assessed PFS, and safety, with a particular focus on bleeding- and infection-related AEs. Other exploratory endpoints included duration of response and time to tumor progression (TTP).

The intent-to-treat (ITT) population included all patients randomized to receive temsirolimus and was the primary population for evaluating all efficacy endpoints and patient characteristics. Safety analyses were conducted on the safety population, which included all patients receiving ≥1 dose of temsirolimus. Analyses were conducted after all patients had at least one-year observation or were off study.

For all time-to-event endpoints, HRs and their 80%CIs were estimated using an unstratified Cox regression model. Because there were no formal statistical hypotheses for this study, *p*-values have not been reported. The median time-to-event was also estimated using the Kaplan–Meier method with two-sided 80%CIs reported for each treatment group. ORR and its exact 80%CI were estimated for each treatment group. The difference in ORR between the two treatment groups was estimated along with exact 80%CI. Safety was evaluated by comparing the incidence of AEs between the two treatment groups.

Results

Patients and treatment

Ninety heavily pretreated patients out of the initially planned 100 patients were randomized and constituted the ITT population; 47 patients in the 175/75-mg group and 43 patients in the 75-mg group. All the 47 (100%) patients in the 75/75-mg group and 42 (97.7%) patients in the 75-mg group received allocated treatment, and constituted the safety population. One (2.3%) patient in the 75-mg group was randomized but not treated. There was a higher percentage of females and patients with five or more prior therapies in the 175/75-mg group. Patient demographics and baseline disease characteristics are shown in Table 1.

At the cutoff date for analysis (12 November 2015), 39 (83.0%) patients in temsirolimus 175/75-mg group and 41 (95.3%) patients in temsirolimus 75-mg group discontinued treatment; the primary reason was objective disease progression in 53.8% versus 56.1% of patients, respectively. Median duration of treatment was comparable in the two temsirolimus groups (3.2 versus 3.1 months, with 175/75 mg versus 75 mg, respectively).

Table 1. Patient demographics and baseline characteristics.

	Temsirolimus dose group		
Characteristic	175/75 mg $n=47$	75 mg $n=43$	Total $N=90$
Age, years			
Mean (SD)	67.0 (8.49)	66.3 (8.47)	66.6 (8.44)
Median (range)	66.0 (47–85)	67.0 (47–86)	67.0 (47–86)
<65, *n* (%)	21 (44.7)	17 (39.5)	38 (42.2)
≥65, *n* (%)	26 (55.3)	26 (60.5)	52 (57.8)
Sex, *n* (%)			
Male	34 (72.3)	36 (83.7)	70 (77.8)
Female	13 (27.7)	7 (16.3)	20 (22.2)
Race, *n* (%)			
White	45 (95.7)	39 (90.7)	84 (93.3)
Asian	2 (4.3)	4 (9.3)	6 (6.7)
Histologic subtype of MCL, *n* (%)			
Blastoid	7 (14.9)	7 (16.3)	14 (15.6)
Nonblastoid	32 (68.1)	30 (69.8)	62 (68.9)
Unknown	8 (17.0)	6 (14.0)	14 (15.6)
Involved disease sites, *n* (%)			
Lymph node	36 (76.6)	38 (88.4)	74 (82.2)
Liver	1 (2.1)	2 (4.7)	3 (3.3)
Spleen	5 (10.6)	3 (7.0)	8 (8.9)
Other	20 (42.6)	17 (39.5)	37 (41.1)
Not reported	5 (10.6)	1 (2.3)	6 (6.7)
Stage at initial diagnosis, *n* (%)			
I	2 (4.3)	2 (4.7)	4 (4.4)
II	1 (2.1)	2 (4.7)	3 (3.3)
III	6 (12.8)	8 (18.6)	14 (15.6)
IV	35 (74.5)	25 (58.1)	60 (66.7)
Other	0	1 (2.3)	1 (1.1)
Unknown	3 (6.4)	5 (11.6)	8 (8.9)
Bone marrow involvement, *n* (%)			
Positive	22 (46.8)	23 (53.5)	45 (50.0)
Negative	21 (44.7)	18 (41.9)	39 (43.3)
Intermediate	1 (2.1)	0	1 (1.1)
Not done	3 (6.4)	2 (4.7)	5 (5.6)
ECOG performance status, *n* (%)			
0	25 (53.2)	20 (46.5)	45 (50.0)
1	17 (36.2)	16 (37.2)	33 (36.7)
2	5 (10.6)	7 (16.3)	12 (13.3)
Number of prior systemic therapies, *n* (%)			
1	0	1 (2.3)	1 (1.1)
2–3	26 (55.3)	29 (67.4)	55 (61.1)
4–5	15 (31.9)	13 (30.2)	28 (31.1)
>5	6 (12.8)	0	6 (6.7)

175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly;
ECOG: Eastern Cooperative Oncology Group; MCL: mantle cell lymphoma; SD: standard deviation.

The median (range) cumulative exposure to study drug over the entire treatment period was 900 (175–12,350) mg in the 175/75-mg group and 500 (75–3750) mg in the 75-mg group. The median (range) number of doses received during the entire study was 10.0 (1–164) and 9.0 (1–55), respectively. The median (range) number of doses received during the first three weeks was 2.0 (1–3) in both groups (Table 2).

Efficacy

The median independently assessed PFS (80%CI) was 4.3 (3.3–6.4) months in the 175/75-mg group versus

Table 2. Drug exposure during the study – safety population.

	Temsirolimus dose group		
	175/75 mg $n = 47$	75 mg $n = 42$	Total $N = 89$
Total dose received during the entire period, mg			
Mean (SD)	1638.9 (2010.6)	843.0 (748.8)	1263.3 (1591.9)
Median (range)	900 (175–12350)	500 (75–3750)	650 (75–12350)
Number of doses received during the entire period			
Mean (SD)	24.9 (35.3)	14.9 (12.9)	20.2 (27.4)
Median (range)	10.0 (1–164)	9.0 (1–55)	10.0 (1–164)
Dose intensity, Weeks 1–3, mg/week			
Mean (SD)	125.0 (43.6)	57.5 (17.6)	93.2 (47.8)
Median (range)	116.7 (53.3–183.8)	53.9 (25.0–78.8)	75.0 (25.0–183.8)
Number of doses received, Weeks 1–3			
Mean (SD)	2.1 (0.7)	2.3 (0.7)	2.2 (0.7)
Median (range)	2.0 (1–3)	2.0 (1–3)	2.0 (1–3)
Patients with dose delay, Weeks 1–3, *n* (%)	28 (59.6)	22 (52.4)	50 (56.2)
Patients with dose reduction, Weeks 1–3, *n* (%)	7 (14.9)	2 (4.8)	9 (10.1)
Dose intensity, Weeks >3, mg/week			
Mean (SD)	52.1 (19.5)	44.1 (18.5)	48.3 (19.3)
Median (range)	58.4 (13.1–77.2)	41.3 (17.7–75.8)	49.0 (13.1–77.2)

175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly; SD: standard deviation.

4.5 (2.7–4.9) months in the 75-mg group (HR 0.731; 80%CI, 0.520–1.027; Figure 1). Although there was no difference in the median PFS, the 75% quartile PFS (80%CI) differed substantially between the 175/75-mg and 75-mg treatment groups (14.9 [8.4–16.4] months versus 7.8 [6.5–11.7] months, respectively). The median investigator-assessed PFS was 4.7 (2.7–8.3) months versus 3.9 (2.8–4.7) months, respectively (HR 0.646; 80%CI, 0.453–0.922; Figure 1), supporting the conclusion that the HR favored the temsirolimus 175/75-mg group with a point estimate <1.

The discordance between PFS in the number of patients deemed as having progressed by the independent review but alive and progression-free by the investigator was eight (17.0%) for the 175/75-mg and three (7.0%) for the 75-mg groups. Similarly, the discordance between PFS in the number of patients deemed as having progressed but alive by the investigator versus progression-free by the independent review was one (2.1%) for the 175/75-mg group and five (11.6%) for the 75-mg group.

Univariate analysis of PFS based on independent assessment by age group, ethnic origin, gender, and geographic region did not show statistical significance for any of these factors. As none of the factors in the univariate analysis were statistically significant, a multivariate analysis was not conducted.

The ORR (80%CI) was 27.7% (19.1–37.7%) in the 175/75-mg group versus 20.9% (13.0–31.0%) in the 75-mg group. The ORR results based on the investigator's assessment were in line with the independent review results (Table 3).

The median duration of response was comparable in both treatment groups (9.0 versus 8.7 months, 175/75 versus 75 mg, respectively). The median TTP (80%CI) was 6.4 (4.4–10.1) months versus 4.8 (3.9–6.5) months, respectively (HR 0.613; 80%CI, 0.415–0.905). The TTP results based on the investigator's assessment were in line with the independent review results.

As of the data cutoff date, 23 (48.9%) patients in the 175/75-mg group and 28 (65.1%) patients in the 75-mg group had died. The median OS (80%CI) was 18.7 (7.5–48.2) months in the 175/75-mg group compared with 11.0 (6.3–16.2) months in 75-mg group (HR 0.681; 80%CI, 0.472–0.982; Figure 2). The 75% quartile OS (80%CI) was 48.2 months with temsirolimus 175/75 mg compared with 19.8 months with temsirolimus 75 mg.

Follow-up therapy

A total of 17 patients in each treatment group (36.2% in the 175/75-mg group and 39.5% in the 75-mg group) received ≥1 systemic therapy after the last dose of temsirolimus. About 60% of all patients did not report any follow-up systemic therapies. The most common systemic follow-up therapy was ibrutinib by 14.9% of patients in the 175/75-mg group and 18.6% of patients in the 75-mg group. The types and number of regimens were generally similar across both treatment groups with the exception of rituximab, which was given at a higher frequency in the 175/75-mg group compared with the 75-mg group (21.3% versus 4.7%, respectively). The number of patients who had radiation therapy and/or surgery after temsirolimus was also well balanced across treatment groups, taking into account that few (<5%) patients had radiation therapy or surgery after temsirolimus treatment ended.

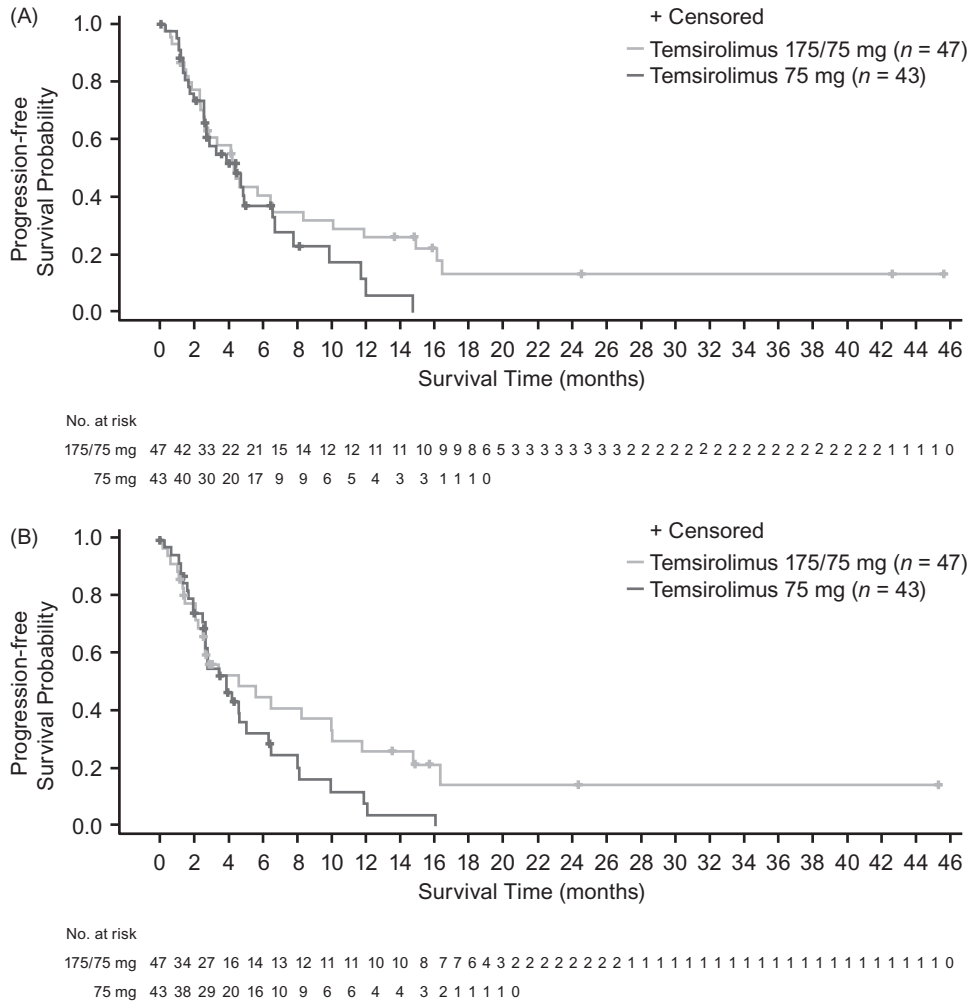

Figure 1. Kaplan–Meier plot of progression-free survival based on independent (A) or investigator (B) assessment: Intent-to-treat population. 175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly.

Table 3. Best overall response – intent-to-treat population.

	Independent assessment		Investigator assessment	
	Temsirolimus dose group		Temsirolimus dose group	
	175/75 mg $n = 47$	75 mg $n = 43$	175/75 mg $n = 47$	75 mg $n = 43$
Complete response, *n* (%)	2 (4.3)	1 (2.3)	2 (4.3)	0
Partial response, *n* (%)	11 (23.4)	8 (18.6)	13 (27.7)	8 (18.6)
Stable disease, *n* (%)	20 (42.6)	22 (51.2)	17 (36.2)	25 (58.1)
Progressive disease, *n* (%)	7 (14.9)	7 (16.3)	10 (21.3)	7 (16.3)
Non-evaluable, *n* (%)	7 (14.9)	5 (11.6)	5 (10.6)	3 (7.0)
Objective response rate (CR + PR), *n* (%)	13 (27.7)	9 (20.9)	15 (31.9)	8 (18.6)
80% exact CI	19.1–37.7	13.0–31.0	22.9–42.2	11.1–28.5
Difference 175/75 versus 75 mg, % (80% CI)	–	6.7 (−6.9, 20.3)	–	13.3 (−0.4, 26.7)

175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly; CI: confidence interval; CR: complete response; PR: partial response.

Safety

Overall, the safety profile was comparable in both treatment groups, although the number of patients with serious AEs, dose reductions, or death was lower in the 175/75-mg versus the 75-mg group, and the number of treatment discontinuations due to AEs was higher with temsirolimus 175/75 mg compared with 75 mg (Table 4). Median (range) time to treatment discontinuation due to AEs was 8.2 (0.1–37.4) weeks in the 175/75-mg group compared with 6.1 (2.1–42.7)

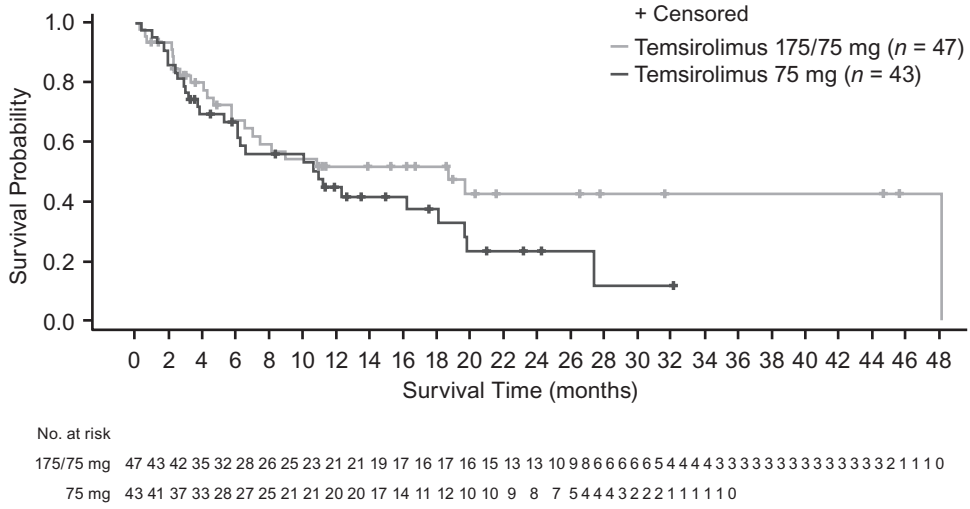

Figure 2. Kaplan–Meier curve of overall survival: Intent-to-treat population. 175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly.

Table 4. Treatment-emergent, all-causality adverse events over entire treatment duration – safety population.

	Temsirolimus dose group	
n (%)	175/75 mg *n* = 47	75 mg *n* = 42
Any adverse event	46 (97.9)	42 (100.0)
Grade ≥3 adverse event	40 (85.1)	35 (83.3)
Serious adverse event	27 (57.4)	31 (73.8)
Adverse event leading to dose delay	41 (87.2)	39 (92.9)
Adverse event leading to dose reduction	23 (48.9)	27 (64.3)
Adverse event leading to discontinuation	9 (19.1)	6 (14.3)
Deaths	11 (23.4)	12 (28. 6)

175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly.

weeks in the 75-mg group. The most common reasons for permanent discontinuation due to AE were dyspnea ($n = 2$: one within the first three weeks and one from the forth week onwards, both in the 175/75-mg group) and pneumonia ($n = 2$: one within the first three weeks in the 175/75-mg group and one from the forth week onwards in the 75-mg group). Other AEs leading to discontinuation included hydrothorax, pulmonary toxicity, respiratory failure, pneumocystis jiroveci pneumonia, headache, neuralgia, myocardial infarction, rectal hemorrhage, hypertriglyceridemia, and skin ulcer ($n = 1$ each). Two of the nine patients in the 175/75-mg group who discontinued due to AEs had died (pneumonia and disease progression).

Treatment-emergent AEs were reported in 46 (97.9%) patients in the 175/75-mg group and for all patients in the 75-mg group (Table 5). Common (>10%) grade ≥3, all-causality, treatment-emergent AEs in the 175/75-mg and 75-mg groups, respectively, were thrombocytopenia (46.8% versus 38.1%), neutropenia (25.5% versus 21.4%), and pneumonia (10.6% versus 19.0%) (Table 5).

Treatment-emergent, bleeding-related AEs of grade ≥2 in the first three weeks occurred in three (6.4%) patients in the 175/75-mg group and one (2.4%) patient in the 75-mg group compared with four (9.5%) and 0 patients, respectively, from the fourth week onwards. The most common treatment-emergent, bleeding-related AEs were epistaxis and ecchymosis in both treatment groups. Only one grade 3 AE of epistaxis that was not related to temsirolimus was reported in the 175/75-mg group, and no grade 3 events were reported in the 75-mg group. Two patients in the 175/75-mg group and one patient in the 75-mg group had treatment-emergent, bleeding-related AEs that resulted in a temporary stop in study drug; no patients in either group had a treatment-emergent, bleeding-related AE that led to treatment discontinuation. One treatment-emergent AE of epistaxis in the 175/75-mg group was assessed to be a serious AE.

Treatment-emergent infection events were comparable across both treatment groups (25.5% of patients in the 175/75-mg group versus 23.8% in the 75-mg group). Pneumonia was the most commonly occurring treatment-emergent, infection-related grade ≥2 AE (12.8% of patients in the 175/75-mg group and 19.0% in the 75-mg group). The number of grade ≥3 events was lower in the 175/75-mg group (14.9%) versus the 75-mg group (21.4%). Treatment-emergent infection events leading to discontinuation were reported for one patient in each group.

Of the 51 deaths reported during the study, the majority of patients died ≥28 days after last dosing. None of the deaths were considered treatment-related and most were due to disease progression ($n = 44$). Other causes of death in the 175/75-mg group

Table 5. Common treatment-emergent, all-causality adverse events experienced by ≥15% of patients – safety population.

	Temsirolimus dose group					
	175/75 mg $n = 47$		75 mg $n = 42$		Total $N = 89$	
Adverse event, *n* (%)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	46 (97.9)	40 (85.1)	42 (100.0)	35 (83.3)	88 (98.9)	75 (84.3)
Thrombocytopenia	32 (68.1)	22 (46.8)	24 (57.1)	16 (38.1)	56 (62.9)	38 (42.7)
Diarrhea	17 (36.2)	1 (2.1)	12 (28.6)	1 (2.4)	29 (32.6)	2 (2.2)
Neutropenia	16 (34.0)	12 (25.5)	11 (26.2)	9 (21.4)	27 (30.3)	21 (23.6)
Dyspnea	11 (23.4)	2 (4.3)	13 (31.0)	2 (4.8)	24 (27.0)	4 (4.5)
Fatigue	11 (23.4)	2 (4.3)	13 (31.0)	4 (9.5)	24 (27.0)	6 (6.7)
Pyrexia	15 (31.9)	3 (6.4)	9 (21.4)	3 (7.1)	24 (27.0)	6 (6.7)
Anemia	10 (21.3)	3 (6.4)	13 (31.0)	3 (7.1)	23 (25.8)	6 (6.7)
Epistaxis	13 (27.7)	1 (2.1)	8 (19.0)	0	21 (23.6)	1 (1.1)
Upper respiratory tract infection	8 (17.0)	2 (4.3)	11 (26.2)	1 (2.4)	19 (21.3)	3 (3.4)
Disease progression	9 (19.1)	9 (19.1)	9 (21.4)	9 (21.4)	18 (20.2)	18 (20.2)
Edema peripheral	8 (17.0)	0	8 (19.0)	1 (2.4)	16 (18.0)	1 (1.1)
Cough	7 (14.9)	0	8 (19.0)	0	15 (16.9)	0
Nausea	6 (12.8)	0	9 (21.4)	2 (4.8)	15 (16.9)	2 (2.2)
Pneumonia	6 (12.8)	5 (10.6)	9 (21.4)	8 (19.0)	15 (16.9)	13 (14.6)
Hypokalemia	6 (12.8)	2 (4.3)	8 (19.0)	2 (4.8)	14 (15.7)	4 (4.5)
Rash	8 (17.0)	0	6 (14.3)	1 (2.4)	14 (15.7)	1 (1. 1)

175/75 mg: temsirolimus 175 mg intravenous dose once-weekly for first 3 weeks, followed by 75 mg intravenous once-weekly; 75 mg: temsirolimus 75 mg intravenous once-weekly.

included pneumonia assessed as unrelated to study drug in one (2.1%) patient who died within 28 days after last dosing. In the 75-mg group, one (2.3%) patient died prior to receiving the study drug; another patient, for unknown reason, died within 28 days after last dosing. One additional patient in the 75-mg group died within 28 days of last dose of temsirolimus due to cardiorespiratory failure. After 28 days of last dosing, one patient in each group died due to unknown reasons, and one (2.3%) patient in the 75-mg group died due to cardiorespiratory failure.

Discussion

Patients with MCL typically develop chemo-resistance during the course of the disease. Despite active treatments for MCL, such as ibrutinib, bortezomib, lenalidomid, and temsirolimus, there is no standard treatment for refractory MCL. The efficacy of temsirolimus in heavily pretreated patients with MCL has been established in a randomized clinical trial wherein temsirolimus 175/75-mg regimen resulted in significant improvements in PFS and ORR compared with the investigator's choice. However, there was a higher incidence of grade ≥3 treatment-emergent AEs and a greater number of AEs leading to dose reduction or delay with temsirolimus 175/75 mg compared with the investigator's choice [8]. It had remained unanswered whether the intensive induction in the 175/75-mg regimen would be beneficial or might be less effective, and if tolerability would be reduced. Therefore, to explore whether similar efficacy but improved safety could be achieved in heavily pretreated patients with relapsed/refractory MCL, we compared two dosing regimens of temsirolimus: 175/75-mg versus a 75-mg dosage.

The benefit-risk assessment for this study centered on the fact that patients in the 175/75-mg group were receiving a regimen that is already approved in Europe for the treatment of relapsed and/or refractory MCL. Patients in the 75-mg group received a dosage regimen that did not include the three starting doses of 175 mg temsirolimus, but had the potential to be safer than the 175/75-mg dosing schedule, while being equally effective. A smaller study with only 29 patients has shown efficacy with lower dose of temsirolimus (25 mg/week); however, these results were not confirmed in a phase III trial [10].

Overall, the primary efficacy endpoint of independently assessed PFS, the secondary efficacy endpoints of ORR and OS, and other secondary endpoints, favored the temsirolimus 175/75-mg treatment. Although no formal statistical conclusions were made, as the study was not powered to detect significant differences between the study groups, the HRs for the investigator-assessed PFS and OS were 0.646 and 0.681, respectively, and the 80%CI excluded 1, suggesting a difference between the two groups. For the endpoints of PFS and OS, the Kaplan–Meier curves began to separate after the median time point in the 175/75-mg group and were in favor of the 175/75-mg regimen (Figures 1 and 2). This suggests the initial loading doses of temsirolimus 175 mg contribute to rapid disease control. The results for the primary endpoint of PFS were comparable to those observed in the previous phase III study of temsirolimus, wherein

median PFS with the 175/75-mg dose was 4.8 months [8] compared with 4.3 months in the current phase IV study. A longer median PFS (6.2 months) with temsirolimus 175/75 mg was achieved in the RAY study, probably because patients included in that study were not as heavily pretreated [11]. ORR in patients receiving 175/75-mg temsirolimus treatment was also comparable between the phase III trial [8] and the current phase IV study (22% and 27.7% of patients, respectively).

In the current study, the overall safety profile across the two treatment groups was comparable, but there was a lower incidence of serious AEs, dose reductions, and deaths in the 175/75-mg group versus the 75-mg group. These safety results are consistent with the known safety profile of temsirolimus [8,12]; no new safety signals were reported. Furthermore, the most commonly occurring grade $\geq$3 AEs in this study (thrombocytopenia and neutropenia) were similar to those reported in two recent studies comparing ibrutinib versus temsirolimus [11] and lenalidomide versus the investigator's choice [13]. Early management of AEs, especially those leading to discontinuation (e.g. dyspnea and pneumonia), is essential to improving patient quality of life and treatment outcome.

Bleeding- and infection-related AEs were of particular interest in this study as they are known to be associated with temsirolimus and other mTOR inhibitors [14,15]. The incidence of treatment-emergent, bleeding-related AEs was higher in the 175/75-mg group versus the 75-mg group, but not during the first 3 weeks of the study (when the loading dose was administered) and the one grade 3 bleeding-related AE was deemed not treatment-related. The incidence of treatment-emergent, infection-related AEs was comparable between treatment groups.

The cumulative evidence across both efficacy and safety measures demonstrated the 175/75-mg temsirolimus regimen was associated with a higher level of efficacy and a similar safety profile compared with the 75-mg regimen. As PFS tended to be longer, more patients remained on treatment and overall drug exposure was higher in the 175/75-mg treatment group. The continued use of the 175/75-mg regimen is justified by the current analysis, especially as the initial phase III trial demonstrated a significant improvement in PFS and ORR with this dosing regimen. Importantly, an early de-escalation in dosage is not associated with improved tolerability.

Treatment landscape has changed since the introduction of temsirolimus within the algorithm of MCL treatment and more treatment options are available today. If and how other therapies work after exposure to temsirolimus is of interest. Therefore, we conducted a follow-up of patients who received other treatments post temsirolimus and found the number of patients who received additional systemic therapy after temsirolimus treatment ended was well balanced across both the 175/75-mg and 75-mg treatment groups (36.2% versus 39.5%, respectively). Also, the types and number of regimens were generally similar across treatment groups, with the exception of rituximab, which was prescribed more frequently to patients in the 175/75-mg group compared with the 75-mg group. Therefore, given that a small proportion of patients receiving follow-up systemic cancer therapy after temsirolimus treatment was generally comparable between treatment groups, we concluded the OS results did not appear to be impacted by post-study treatment for MCL.

The higher response rate and longer median PFS, respectively, demonstrated with ibrutinib (72% and 14.6 months) [11] and lenalidomide (40% and 8.7 months) [13] in patients with MCL, and their oral administration, would probably position them as a preferable treatment before temsirolimus and other mTOR inhibitors. Nonetheless, the PI3K/Akt/mTOR pathway is an important therapeutic target in MCL because it is consistently dysregulated and contributes to MCL pathogenesis [16]. Inhibitors of the PI3K/Akt/mTOR pathway, including temsirolimus, everolimus and idelalisib have demonstrated clinical benefit in relapsed/refractory MCL [8,17,18]. In our study, temsirolimus demonstrated clinical benefit in heavily pretreated patients with relapsed/refractory MCL. Because none of these agents is curative as a single agent, they should be investigated in combination with other agents to enhance their activity. Indeed, several phase I/II studies demonstrated high response rate with temsirolimus in combination with rituximab and chemotherapy [19–21].

In conclusion, PFS, ORR, and OS favored the temsirolimus 175/75-mg regimen over the 75-mg regimen, although no formal statistical conclusions were made, as the study was not powered to detect significant differences between study groups. The safety profile in both study groups was comparable, but there was a lower incidence of serious AEs, dose reductions, and deaths in the 175/75-mg group. Consequently, temsirolimus 175/75 mg remains the preferred dosing regimen for patients with relapsed/refractory MCL and additional combination studies should be investigated.

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References

[1] Cortelazzo S, Ponzoni M, Ferreri AJ, et al. Mantle cell lymphoma. Crit Rev Oncol Hematol. 2012;82:78–101.
[2] Non-Hodgkin Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group. Blood. 1997;89:3909–3918.
[3] Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol. 2005;131:29–38.
[4] Argatoff LH, Connors JM, Klasa RJ, et al. Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood. 1997;89:2067–2078.
[5] Campo E, Raffeld M, Jaffe ES. Mantle-cell lymphoma. Semin Hematol. 1999;36:115–127.
[6] Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111:558–565.
[7] Lai R, Medeiros LJ. Pathologic diagnosis of mantle cell lymphoma. Clin Lymphoma. 2000;1:197–206. discussion 207-198.
[8] Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009;27:3822–3829.
[9] Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin lymphomas. NCI Sponsored International Working Group. JCO. 1999;17:1244.
[10] Ansell SM, Inwards DJ, Rowland KM, Jr, et al. Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group. Cancer. 2008;113:508–514.
[11] Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016;387:770–778.
[12] Hess G, Coiffier B, Crump M, et al. Effect of prognostic classification on temsirolimus efficacy and safety in patients with relapsed or refractory mantle cell lymphoma: a retrospective analysis. Exp Hematol Oncol. 2015;4:11.
[13] Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol. 2016;17:319–331.
[14] European Medicines Agency. Torisel® (temsirolimus) summary of product characteristics. 2009 [cited 2017 Mar 27]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000799/human_med_001098.jsp&mid=WC0b01ac058001d124.
[15] Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev (Orlando). 2014;28:126–133.
[16] Smith SM. Targeting mTOR in mantle cell lymphoma: current and future directions. Best Pract Res Clin Haematol. 2012;25:175–183.
[17] Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kδ inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). Blood. 2014;123:3398–3405.
[18] Renner C, Zinzani PL, Gressin R, et al. A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma. Haematologica. 2012;97:1085–1091.
[19] Ansell SM, Tang H, Kurtin PJ, et al. Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphoma: a phase 2 study. Lancet Oncol. 2011;12:361–368.
[20] Hess G, Keller U, Scholz CW, et al. Safety and efficacy of Temsirolimus in combination with Bendamustine and Rituximab in relapsed mantle cell and follicular lymphoma. Leukemia. 2015;29:1695–1701.
[21] Inwards DJ, Fishkin PA, LaPlant BR, et al. Phase I trial of rituximab, cladribine, and temsirolimus (RCT) for initial therapy of mantle cell lymphoma. Ann Oncol. 2014;25:2020–2024.