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ORIGINAL REPORT

Phase III Study to Evaluate Temsirolimus Compared With Investigator's Choice Therapy for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Temsirolimus, a specific inhibitor of the mammalian target of rapamycin kinase, has shown clinical activity in mantle cell lymphoma (MCL). We evaluated two dose regimens of temsirolimus in comparison with investigator's choice single-agent therapy in relapsed or refractory disease.

Patients and Methods
In this multicenter, open-label, phase III study, 162 patients with relapsed or refractory MCL were randomly assigned (1:1:1) to receive one of two temsirolimus regimens: 175 mg weekly for 3 weeks followed by either 75 mg (175/75-mg) or 25 mg (175/25-mg) weekly, or investigator's choice therapy from prospectively approved options. The primary end point was progression-free survival (PFS) by independent assessment.

Results
Median PFS was 4.8, 3.4, and 1.9 months for the temsirolimus 175/75-mg, 175/25-mg, and investigator's choice groups, respectively. Patients treated with temsirolimus 175/75-mg had significantly longer PFS than those treated with investigator's choice therapy ($P = .0009$; hazard ratio = 0.44); those treated with temsirolimus 175/25-mg showed a trend toward longer PFS ($P = .0618$; hazard ratio = 0.65). Objective response rate was significantly higher in the 175/75-mg group (22%) compared with the investigator's choice group (2%; $P = .0019$). Median overall survival for the temsirolimus 175/75-mg group and the investigator's choice group was 12.8 months and 9.7 months, respectively ($P = .3519$). The most frequent grade 3 or 4 adverse events in the temsirolimus groups were thrombocytopenia, anemia, neutropenia, and asthenia.

Conclusion
Temsirolimus 175 mg weekly for 3 weeks followed by 75 mg weekly significantly improved PFS and objective response rate compared with investigator's choice therapy in patients with relapsed or refractory MCL.

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INTRODUCTION

Mantle cell lymphoma (MCL) accounts for 5% to 10% of all B-cell non-Hodgkin's lymphomas, is associated with poor prognosis, and remains incurable with standard chemotherapy approaches.[1,2] Although for first- or second-line therapy, combination chemotherapy regimens like cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) or rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) and/or high-dose consolidation therapy are frequently used,[3-7] long-term remissions are rare. After failure of first- or second-line treatments, various single agents are used, despite limited response rates and short remission duration.[3,8-15] Thus despite improvements in other lymphoma subtypes, in MCL, there is still a strong unmet medical need for new treatment options.

On a molecular level, MCL is driven by the chromosomal translocation t(11;14) (q13;q32) resulting in overexpression of cyclin D1 mRNA.[16] Translation of cyclin D1 mRNA was hypothesized to be regulated by the mammalian target of rapamycin (mTOR) kinase, a key component of the PI3K/AKT pathway.[17] On the basis of this hypothesis, temsirolimus, a specific inhibitor of the mTOR kinase,[18,19] was evaluated in patients with MCL.[20,21] In two phase II studies, treatment with

temsirolimus (250 mg or 25 mg weekly) resulted in similar frequencies of complete and partial responses in a heavily pretreated population. However, there was reduced toxicity with the 25-mg dose, primarily less thrombocytopenia.

Here, we report the results of a randomized, open-label, phase III study in patients with relapsed or refractory MCL. To explore a dose-response relationship, two different dose regimens of temsirolimus were chosen, and each was compared with prospectively approved investigator's choice therapy. The composition of the competitor arm was chosen to reflect daily practice and, therefore, allowed clinically relevant comparison of the experimental arms with established treatment options. Each temsirolimus regimen used 175 mg per week for 3 weeks, based on the initial median dose of 175 mg per week delivered in the previous phase II testing of the 250-mg regimen.[22] After the initial 175-mg doses, temsirolimus was administered in weekly doses of 25 mg or 75 mg.

PATIENTS AND METHODS

Patients

Patients at least 18 years of age were required to have refractory and/or relapsed MCL after two to seven prior therapies. All reasonable alternatives with combination therapy should have been exhausted before including a patient in this study. Pretreatment must have included an alkylating agent, an anthracycline, and rituximab, and could have included hematopoietic stem-cell transplantation. MCL had to be confirmed at the investigational site by histology, immunophenotype, and cyclin D1 analysis. This was reevaluated centrally during the conduct of the study. Patients also were required to have a life expectancy of at least 3 months, a Karnofsky performance score of 60 or higher, measurable disease, and adequate bone marrow and organ functions (absolute neutrophil count [ANC] $\geq$ 1,000/μL; platelet count $\geq$ 75,000/μL or $\geq$ 50,000/μL if bone marrow involved; hemoglobin level $\geq$ 8 g/dL; serum creatinine $\leq$ 2$\times$ the upper limit of the normal range [ULN]; AST level $\leq$ 3$\times$ ULN or $\leq$ 5$\times$ ULN if liver involved; total bilirubin level $\leq$ 1.5$\times$ ULN; fasting serum cholesterol level $\leq$ 350 mg/dL; triglyceride level $\leq$ 400 mg/dL; and other laboratory values $\leq$ grade 2 of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, unless related to lymphomatous organ involvement). Patients with active CNS lymphoma, HIV or hepatitis B or C virus infections, and anticancer treatment or major surgery within 3 weeks before the first drug administration were excluded.

The study protocol was approved by the institutional review boards of all participating centers, and the study was conducted in accordance with international standards of good clinical practice. All patients provided written informed consent.

Treatment

The two temsirolimus groups each initially received intravenous drug 175 mg per week for 3 weeks followed by weekly doses of either 75 mg or 25 mg (175/75-mg or 175/25-mg, respectively). These 75-mg and 25-mg doses were chosen because they were previously shown to be well tolerated and have antitumor activity in other tumor types, including renal cell carcinoma[23] and breast cancer.[24] In addition, emerging data from the phase II MCL study indicated that the 25-mg dose was potentially as active as a higher dose but better tolerated.[25] The 75-mg dose also was chosen because it yielded exposures in blood that could be distinguished from the 25-mg dose, which allowed investigation of a dose-response effect. The investigator's choice therapy group received single-agent treatment as chosen by the investigator (Table 1). These single agents were protocol specified or prospectively approved additions. They were selected after an extensive review of the literature and discussions with a large number of investigators. Agents had to be widely available for the treatment of MCL at the time of study inception.

Temsirolimus (Wyeth Pharmaceuticals, Philadelphia, PA) was administered as an intravenous infusion over 30 to 60 minutes. Approximately 30 minutes before the start of the infusion, patients received antihistamine premedication. In case of hypersensitivity reaction, adequate measures had to be undertaken before reinitiation of treatment. Concomitant treatment with corticosteroids was not allowed.

Temsirolimus treatment was continued until disease progression or unacceptable toxicity. It was withheld for ANC less than 1,000/μL, platelet counts less than 50,000/μL, or grade 3 or 4 nonhematologic adverse events (AEs). Treatment was reinitiated at a reduced dose if patients recovered ANC to $\geq$ 1,000/μL, platelet counts to $\geq$ 50,000/μL, or nonhematologic AEs to grade 0 to 2 within 3 weeks. Dose reductions for toxicity from 175 mg were to 75 mg or 25 mg, depending on the treatment group. Thereafter, for the 175/75-mg group, a maximum of two dose reductions from 75 mg to 50 mg and 25 mg was allowed. For the 175/25-mg group, a single dose reduction from 25 mg to 15 mg was allowed.

Evaluation

CBC, serum chemistry, and AEs were monitored at regular intervals. An independent data monitoring committee reviewed study conduct and safety data at least every 6 months.

Complete disease assessments and computed tomographic scans of the neck, chest, abdomen, and pelvis were performed approximately every 8 weeks during year 1, every 12 weeks during year 2, and then every 6 months until disease progression or initiation of new anticancer therapy. Tumor response

Table 1. Therapies Used in the Investigator's Choice Group

Therapy	Description	No. of Patients (n = 53)	%
Gemcitabine IV[9,26]	(a) 1 g/m^2 as 30-minute infusion on days 1, 8, and 15 every 28 days, or (b) 1 g/m^2 as 30-minute infusion on days 1 and 8 every 21 days	22	42
Fludarabine IV[8]	25 mg/m^2 as 30-minute infusion daily for 5 consecutive days every 28 days	12	23
Fludarabine oral[27]	40 mg/m^2 daily for 5 consecutive days every 28 days	2	4
Chlorambucil oral[28]	0.1 to 0.2 mg/kg daily for 3 to 6 weeks	3	6
Cladribine IV[29]	5 mg/m^2 daily for 5 consecutive days every 28 days (1 cycle) for 2 to 6 cycles	3	6
Etoposide IV[26]	50 to 150 mg/m^2 daily for 3 to 5 days every 21 to 28 days	3	6
Cyclophosphamide oral[26]	200 to 450 mg/m^2 daily for 5 consecutive days every 21 to 28 days	2	4
Thalidomide oral[30]	200 mg daily	2	4
Vinblastine IV[31]	10 mg weekly	2	4
Alemtuzumab IV[32]	30 mg/d for 3 times a week on alternate days for 12 weeks	1	2
Lenalidomide oral[33]	25 mg daily for 28 days	1	2

Abbreviation: IV, intravenous.

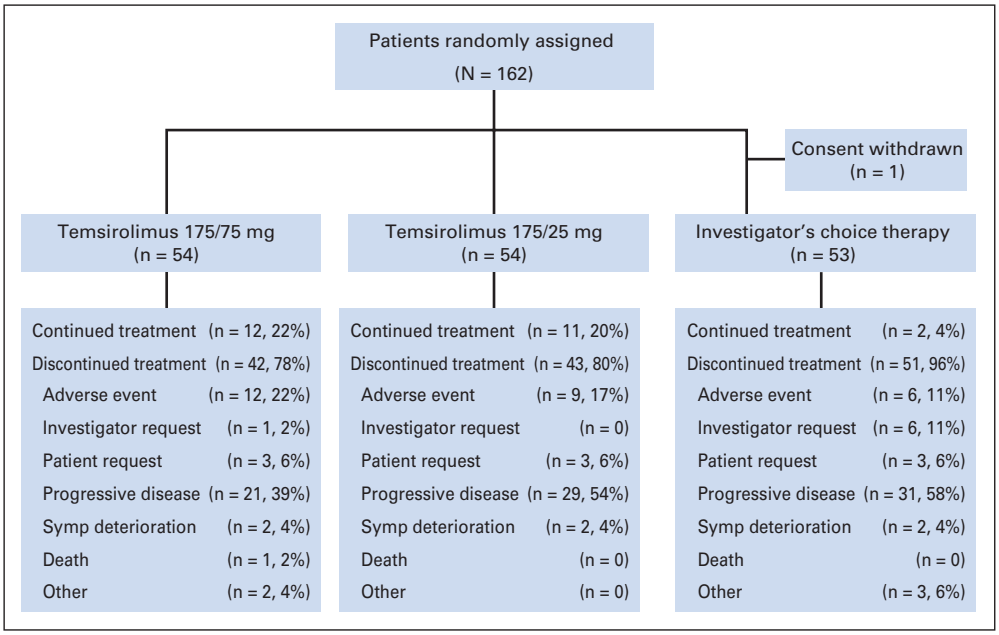

Fig 1. Enrollment and outcomes of patients in the intent-to-treat population as of the time of primary data analysis, July 19, 2007. Investigator request included decisions by investigators to complete, stop, or change treatment. Symp deterioration, symptomatic deterioration.

was assessed with the use of the Modified Criteria for Non-Hodgkin's Lymphoma.[34] Both investigator assessment and central independent assessment (RadPharm, Princeton, NJ) were made using radiologic and clinical data.

Statistical Analysis

The primary efficacy end point of the study was progression-free survival (PFS), as assessed by independent review and calculated for the intent-to-treat population, which included all patients randomly assigned before July 19, 2007. PFS was defined as the time from the date of randomization to the earlier date of either disease progression or death from any cause (if within 4 months of the last valid tumor assessment), censored at the last valid tumor assessment.[35] To detect a hazard ratio (HR) of 0.48 for the comparison of PFS of each temsirolimus group versus the investigator's choice group at 80% power using a two-sided log-rank test at the 2.5% significance level (assuming medians of 6.2 and 3.0 months, respectively), a total of 105 events had to be observed.

Secondary efficacy end points were PFS, as assessed by investigators; objective response rate; and overall survival. Objective response rate was defined as the percentage of patients who had complete, complete unconfirmed, or partial response, based on independent assessment. Overall survival was defined as the time from the date of randomization to death from any cause. All patients who received any treatment were included in the analysis of safety.

Results for time-to-event end points were analyzed according to Kaplan-Meier estimates and an unstratified Cox proportional hazards model. Comparisons of baseline characteristics, objective response rates, and incidences of AEs between treatment groups were made using Fisher's exact test.

RESULTS

From June 2005 to July 2007, 162 patients from 70 sites were randomly assigned to receive temsirolimus 175/75-mg or 175/25-mg or investigator's choice therapy (Fig 1). One patient enrolled in the investigator's choice group requested not to receive treatment.

Patient Characteristics

The baseline characteristics of the intent-to-treat population are shown in Table 2. The three treatment groups were generally well balanced. However, 0, nine, and four patients had blastoid histology in the temsirolimus 175/75-mg, 175/25-mg, and investigator choice groups, respectively. The median number of prior treatment regimens was three for the temsirolimus groups and four for the investigator's choice group. The median number of prior rituximab and other anti-CD20 immunotherapy regimens was two for each treatment group. Approximately 32% of patients in each group had prior hematopoietic stem-cell transplantation.

Efficacy

Primary end point. At the time of primary data analysis, July 19, 2007, 105 patients (29, 38, and 38 in the temsirolimus 175/75-mg, 175/25-mg, and investigator's choice groups, respectively) had experienced disease progression or died within 4 months of the last valid tumor assessment. Patients treated with temsirolimus 175/75-mg had significantly longer PFS than those treated with investigator's choice therapy ($P = .0009$; Fig 2A, Table 3). Patients treated with temsirolimus 175/25-mg showed a trend toward longer PFS than those treated with investigator's choice therapy ($P = .0618$). Median PFS in the temsirolimus 175/75-mg, 175/25-mg, and investigator's choice groups was 4.8, 3.4, and 1.9 months, respectively. For the comparison of treatment with temsirolimus 175/75-mg with investigator's choice therapy, the HR for progression was 0.44 (97.5% CI, 0.25 to 0.78). For the comparison of treatment with temsirolimus 175/25-mg with investigator's choice therapy, the HR was 0.65 (97.5% CI, 0.39 to 1.10).

In exploratory subgroup analyses using an unstratified Cox proportional hazards model, no significant differences in efficacy with respect to PFS of temsirolimus 175/75-mg or 175/25-mg and investigator's choice therapies were observed based on age (≤ 65 years), sex, baseline Karnofsky performance score, stage of disease at diagnosis, bone marrow involvement, number of extranodal sites, and number of prior regimens of anticancer therapy ($P > .15$). Importantly, after the exclusion of patients with blastoid histology, results of statistical analyses remained unchanged (data not shown), so it seems unlikely that the unbalanced distribution influenced the trial results. For patients with fewer than three prior regimens in the temsirolimus 175/

Table 2. Baseline Patient Characteristics

Characteristic	Temsirolimus 175/75-mg (n = 54)		Temsirolimus 175/25-mg (n = 54)		Investigator's Choice (n = 54)		Total (N = 162)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	68		68.5		64.5		67	
Range	44-87		43-85		39-88		39-88	
Male sex	46	85	40	74	46	85	132	81
Karnofsky performance score								
60 or 70	10	19	8	15	6	11	24	15
≥ 80	44	81	45	83	48	89	137	85
Missing	0		1		0		1	
Primary diagnosis								
MCL	46	85	45	83	45	83	136	84
NHL	0		3	6	1	2	4	3
Unconfirmed MCL*	8	15	6	11	8	15	22	14
Bone marrow involvement	24	44	29	54	21	39	74	46
Time from first diagnosis to randomization, months								
Mean	49.6		47.7		48.3		48.5	
Range	10-151		5-216		5-159		5-216	
Stage of disease at baseline								
II	0		2	4	3	6	5	3
III, IV	54	100	52	96	51	94	157	97
Histology grade								
Blastoid	0		9	17	4	7	13	8
Typical	46	85	35	65	40	74	121	75
Unknown*	8	15	10	19	10	19	28	17
Prior hematopoietic stem cell transplantation	17	32	15	28	20	37	52	32
No. of prior regimens								
2-3	28	52	32	59	21	39	81	50
4-7	26	48	22	41	33	61	81	50
No. of prior immunotherapy regimens								
1-2	34	63	42	78	36	67	112	69
3-6	19	35	9	17	15	28	43	27
Therapy type not reported	1	2	3	6	3	6	7	4
Prior bortezomib therapy	10	19	10	19	17	31	37	23

Abbreviations: MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma.
*Mantle cell lymphoma was diagnosed based on histology, immunophenotype, and cyclin D1 analysis at the local sites, but samples were insufficient or of poor quality for independent assessment.

75-mg, 175/25-mg, and investigator's choice groups, median PFS was 7.4, 3.4, and 1.6 months, respectively; for patients with three or more prior regimens, median PFS was 4.5, 3.4, and 2.0 months, respectively.

Secondary end points. The objective response rate in the temsirolimus 175/75-mg group was significantly higher than that observed in the investigator's choice group (22% *v* 2%; $P = .0019$; Table 3), but the objective response rate in the 175/25-mg group was not (6%; $P = .6179$).

As of July 19, 2007, patients treated with temsirolimus 175/75-mg and 175/25-mg had median overall survival of 11.1 and 8.8 months, respectively, compared with the median overall survival of 9.5 months for investigator's choice therapy ($P = .3053$ and 0.9515, respectively; Table 3). Additional data on overall survival were collected through February 1, 2008. At this time, patients treated with temsirolimus 175/75-mg and 175/25-mg had median overall survival of 12.8 and 10.0 months, respectively, compared with the median overall survival of 9.7 months for investigator's choice therapy ($P = .3519$ and 0.8714, respectively; Fig 2B; Table 3).

Safety

The duration of treatment was longer for the temsirolimus groups than for the investigator's choice group (temsirolimus 175/75-mg, median, 12 weeks [range, 1 to 97 weeks]; temsirolimus 175/25-mg, median, 14 weeks [range, 1 to 172 weeks]; investigator's choice, median, 5 weeks [range, 1 to 35 weeks]). For the three initial 175-mg doses of temsirolimus, the mean relative dose-intensities (actual total doses/assigned total doses) were 0.74 and 0.70 for the 175/75-mg and 175/25-mg groups, respectively. For the subsequent doses of 75 mg and 25 mg, the mean relative dose-intensities were 0.69 and 0.86, respectively.

Of the 162 patients in the intent-to-treat population, 161 patients were assessable for safety. The most common AEs that occurred in the temsirolimus groups were thrombocytopenia, asthenia, anemia, diarrhea, and fever (Table 4). Thrombocytopenia, asthenia, and diarrhea occurred with a significantly higher incidence in the temsirolimus groups than in the investigator's choice group ($P \leq .041$). Leukopenia was the only AE that occurred with

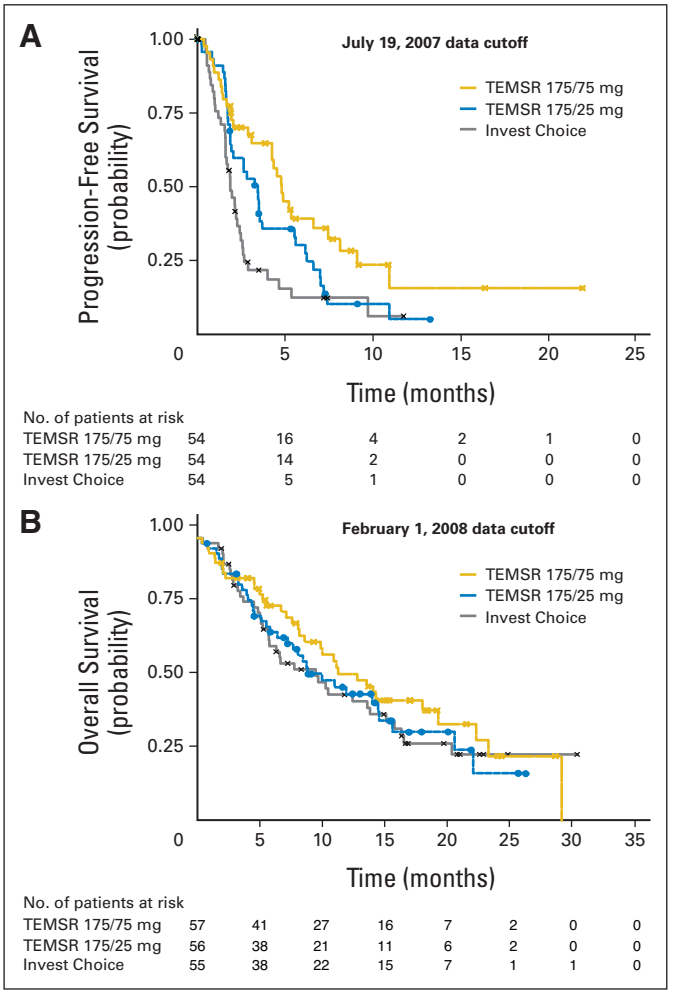

Fig 2. Kaplan-Meier estimates of (A) progression-free survival, independent assessment and (B) overall survival. Censored patients are indicated (x, o). TEMSR, temsirolimus; Invest Choice, investigator's choice.

a significantly higher incidence in the investigator's choice group ($P \leq .036$).

Grade 3 or 4 AEs occurred in 89% of patients in the temsirolimus 175/75-mg group, 80% of patients in the 175/25-mg group, and 68% of patients in the investigator's choice group. The most common grade 3 or 4 AEs that occurred in the temsirolimus groups were thrombocytopenia, anemia, neutropenia, and asthenia (Table 4). Only thrombocytopenia occurred with a significantly higher incidence in the temsirolimus group (175/75-mg) than in the investigator's choice group ($P = .020$). Grade 3 or 4 leukopenia occurred with a significantly higher incidence in the investigator's choice group ($P \leq .014$).

DISCUSSION

With current treatment approaches, MCL remains an incurable disease, and refractoriness to available therapy options is frequently observed late in its course. Therefore, new treatment approaches are needed. We compared temsirolimus in two different dose regimens (175/75-mg and 175/25-mg) with investigator's choice therapy for heavily pretreated patients with MCL. PFS by independent assessment, the primary end point, was significantly longer for the temsirolimus 175/75-mg group than for the investigator's choice group ($P = .0009$; HR = 0.44) and showed a trend toward improvement in the temsirolimus 175/25-mg group compared with the investigator's choice group ($P = .0618$; HR = 0.65). The objective response rate, a secondary end point, was significantly higher for the temsirolimus 175/75-mg group than for the investigator's choice group ($P = .0019$), but was not for the temsirolimus 175/25-mg group. Thus there was a dose-response relationship between these two temsirolimus dose regimens and antitumor activity in MCL.

For the temsirolimus regimens, the 175-mg dose was administered initially for 3 weeks to maximize antitumor activity. Although more patients who were treated with the 75-mg dose had dose reductions than those treated with the 25-mg dose (mean relative dose-intensities of 0.69 and 0.86, respectively), the efficacy observed for the 75-mg dose and the fact that AE profiles were similar for both doses support the conclusion that 75 mg should be the recommended dose for continuation of treatment. The observed dose-response relationship could be especially valuable for the future development of temsirolimus in other lymphoma entities, where promising efficacy was recently demonstrated.[36]

This study was not powered to detect a difference in overall survival because the number of patients required would have precluded completion of enrollment within a reasonable time period. Furthermore, subsequent anticancer therapies may have had an impact on the overall survival results. A greater percentage of patients in the investigator's choice group than in the temsirolimus 175/75-mg and 175/25-mg groups received subsequent anticancer therapy (70%, 41%, and 46%, respectively), including bortezomib (22%, 7%, and 13%, respectively).

Within our study, the efficacy results for the investigator's choice group were poor. Although a number of different regimens were available, the drugs used most frequently were gemcitabine and fludarabine (42% and 26% of patients, respectively). In published phase II studies with these drugs, objective response rates of 15% to 30% were obtained.[8,9,27] These rates are in marked contrast to the 2% rate that we observed. These differences likely reflect the fact that patients in our study had received more prior treatment regimens, because it is frequently observed in MCL that objective response rates rapidly decrease as the number of treatment regimens increases.

In the phase II temsirolimus studies of patients with relapsed, refractory MCL, objective response rates of 38% and 41% were obtained for the 250-mg and 25-mg weekly regimens, respectively.[20,21] The objective response rate of 22% for our study seems lower, but may also be due to differences in the patients in the current study and in the phase II studies. In the latter, patients were not required to have had prior treatment with an anthracycline, an alkylating agent, and an anti–CD20-antibody containing regimen.

This is the only randomized phase III study of a single agent in relapsed or refractory MCL. We demonstrated the value of mTOR inhibition in a lymphoma subtype where this pathway is thought to be integral to pathogenesis. Furthermore, temsirolimus was compared with a competitor arm that was composed of treatment options used in daily practice and, therefore, a practical interpretation and use of the results is possible. With the promising efficacy of single-agent temsirolimus in follicular and diffuse large-cell lymphoma,[36] our data can guide the evaluation of mTOR inhibitors in patients with other B-cell non-Hodgkin's lymphomas.

Table 3. Summary of Efficacy Measures

Parameter	Temsirolimus 175/75-mg (n = 54)	Temsirolimus 175/25-mg (n = 54)	Investigator's Choice (n = 54)
Progression-free survival, independent assessment			
Median, months	4.8	3.4	1.9
97.5% CI	3.1 to 8.1	1.9 to 5.5	1.6 to 2.5
HR*†	0.44	0.65	
97.5% CI	0.25 to 0.78	0.39 to 1.10	
*P**‡	.0009	.0618	
Progression-free survival, investigator assessment			
Median, months	4.8	3.7	1.8
95% CI	2.9 to 7.0	3.4 to 6.2	1.6 to 2.0
HR*†	0.39	0.41	
95% CI	0.25 to 0.63	0.26 to 0.65	
*P**‡	< .0001	< .0001	
Overall survival (as of July 19, 2007)			
Median, months	11.1	8.8	9.5
95% CI	8.2 to 18.0	6.4 to 14.5	5.3 to 15.1
HR*†	0.77	0.98	
95% CI	0.46 to 1.28	0.60 to 1.62	
*P**‡	.3053	.9515	
Overall survival (as of February 1, 2008)§			
Median, months	12.8	10.0	9.7
95% CI	8.6 to 19.3	7.2 to 14.6	5.8 to 15.1
HR*†	0.80	0.96	
95% CI	0.50 to 1.28	0.60 to 1.54	
*P**‡	.3519	.8714	
Tumor response, independent assessment			
Complete response			
No.	1	0	1
%	2		2
Partial response			
No.	11	3	0
%	20	6	
Objective response rate, %	22	6	2
95% CI	11 to 33	0 to 12	0 to 5
*P**‖	.0019	.6179	
Time to response, independent assessment			
Median, months	3.6	3.5	4.0
95% CI	3.5 to 4.0	3.5 to 4.1	NA
HR*†	1.11	1.14	
95% CI	0.14 to 9.01	0.10 to 13.3	
*P**‡	.9422	.9183	
Duration of response, independent assessment			
No. patients with end of response	5	6	0
Median, months	7.1	3.6	NA
95% CI	4.1 to NA	3.2 to 10.6	
HR*†	NA	NA	
95% CI			
*P**‡	.3104	.3621	

Abbreviations: HR, hazard ratio; NA, not available.
*Temsirolimus group: investigator's choice group.
†Cox proportional hazards model.
‡Log-rank test.
§n = 57, 56, and 55 for temsirolimus 175/75-mg, 175/25-mg, and investigator's choice groups, respectively.
‖Fisher's exact test.

Phase II trials of other agents for the treatment of MCL have included different criteria for patient selection. Rituximab was evaluated in patients with newly diagnosed or early relapsed disease; a response rate of 28% to 37% was observed.[10,37] Bortezomib was evaluated in patients with a maximum of two prior treatments (median, one regimen); a response rate of 33% in 141 assessable patients was observed.[38] Further studies are needed to directly compare the efficacy of these agents with that of temsirolimus in a comparable patient population.

The most common AE was thrombocytopenia, which also was observed in patients with renal cell carcinoma treated with temsirolimus, although with a lower incidence.[39] Thrombocytopenia is more

Table 4. Adverse Events Occurring in More Than 20% of Patients in Any Group

Adverse Event	% of Patients					
	Temsirolimus 175/75-mg (n = 54)		Temsirolimus 175/25-mg (n = 54)		Investigator's Choice (n = 53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Thrombocytopenia	72	59	82	52	53	36
Asthenia	63	13	57	19	26	8
Anemia	52	20	52	11	43	17
Diarrhea	44	7	33	11	9	0
Fever	39	6	37	2	30	0
Anorexia	37	2	28	2	15	2
Mucositis	35	6	17	2	0	0
Epistaxis	35	0	24	0	6	0
Rash	35	7	26	2	9	0
Infection	28	9	22	4	9	4
Pain	28	2	19	2	4	2
Chills	26	2	9	0	13	2
Nausea	26	0	26	0	21	0
Cough increased	26	0	30	2	9	2
Pruritus	26	4	19	0	6	0
Neutropenia	24	15	32	22	40	26
Peripheral edema	22	2	19	6	15	0
Abdominal pain	20	2	22	4	15	0
Dyspnea	19	7	20	9	28	9
Leukopenia	15	7	20	9	40	28

commonly observed in the MCL population than in the renal cell carcinoma population because, in the former, bone marrow is involved in the disease and is compromised from prior cytotoxic therapy. Although thrombocytopenia was pronounced in patients treated with temsirolimus 175/75-mg and 175/25-mg and grade 1 or 2 epistaxis was observed in 35% and 24% of patients, respectively, this was clinically manageable. The only grade 3 bleeding event was a rectal hemorrhage, which occurred in a patient who had received 330 mg, rather than 175 mg, as the first two doses of temsirolimus due to a medication error.

Less common but important AEs included neutropenic fever in two patients who received temsirolimus. Only one case of grade 3 or 4 interstitial pneumonia was reported, although the increased cough observed in the temsirolimus groups might be due to undiagnosed, mild interstitial pneumonitis. Additional evaluation of patients for pulmonary toxicity is warranted in future studies.

Our data demonstrate that, for heavily pretreated patients with MCL, temsirolimus 175/75-mg conferred a statistically significant improvement in PFS and objective response rate in comparison with standard chemotherapeutic single agents. As results seem to be more distinct for patients with less intensive pretreatment, the true benefit for patients with MCL, in part, may have been masked by the patient selection in this trial. Therefore, future trials will address the efficacy in earlier disease and tolerability and efficacy of combination regimens.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. The Non-Hodgkin's Lymphoma Classification Project: A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 89:3909-3918, 1997

2. Argatoff LH, Connors JM, Klasa RJ, et al: Mantle cell lymphoma: A clinicopathologic study of 80 cases. Blood 89:2067-2078, 1997

3. Cohen BJ, Moskowitz C, Straus D, et al: Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 42:1015-1022, 2001

4. Evens AM, Winter JN, Hou N, et al: A phase II clinical trial of intensive chemotherapy followed by consolidative stem cell transplant: Long-term follow-up in newly diagnosed mantle cell lymphoma. Br J Haematol 140:385-393, 2008

5. Lenz G, Dreyling M, Hiddemann W: Mantle cell lymphoma: Established therapeutic options and future directions. Ann Hematol 83:71-77, 2004

6. Pott C, Schrader C, Gesk S, et al: Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. Blood 107:2271-2278, 2006

7. Romaguera JE, Fayad L, Rodriguez MA, et al: High rate of durable remissions after treatment of newly diagnosed aggressive mantle cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 23:7013-7023, 2005

8. Decaudin D, Bosq J, Tertian G, et al: Phase II trial of fludarabine monophosphate in patients with mantle- cell lymphomas. J Clin Oncol 16:579-583, 1998

9. Dumontet C, Morschhauser F, Solal-Celigny P, et al: Gemcitabine as a single agent in the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma. Br J Haematol 113:772-778, 2001

10. Ghielmini M, Schmitz SFH, Cogliatti S, et al: Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: A study of the Swiss Group for Clinical Cancer Res (SAKK). J Clin Oncol 23:705-711, 2005

11. Kouroukis CT, Belch A, Crump M, et al: Flavopiridol in untreated or relapsed mantle cell lymphoma: Results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:1740-1745, 2003

12. Lenz G, Hiddemann W, Dreyling M: The role of fludarabine in the treatment of follicular and mantle cell lymphoma. Cancer 101:883-893, 2004

13. Weigert O, Unterhalt M, Hiddemann W, et al: Current management of mantle cell lymphoma. Drugs 67:1689-1702, 2007

14. Zinzani PL, Magagnoli M, Moretti L, et al: Fludarabine-based chemotherapy in untreated mantle cell lymphomas: An encouraging experience in 29 patients. Haematologica 84:1002-1006, 1999

15. Zinzani PL, Magagnoli M, Moretti L, et al: Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle cell lymphoma. J Clin Oncol 18:773-779, 2000

16. Jares P, Colomer D, Campo E: Genetic and molecular pathogenesis of mantle cell lymphoma: Perspectives for new targeted therapeutics. Nat Rev Cancer 7:750-762, 2007

17. Witzig TE, Kaufmann SH: Inhibition of the phosphoinositol 3-kinase/mammalian target of rapamycin pathway in hematologic malignancies. Curr Treat Options Oncol 7:285-294, 2006

18. Bjornsti MA, Houghton PJ: The TOR pathway: A target for cancer therapy. Nat Rev Cancer 4:335-348, 2004

19. Faivre S, Kroemer G, Raymond E: Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov 5:671-688, 2006

20. 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 113:508-514, 2008

21. Witzig TE, Geyer SM, Ghobrial I, et al: Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol 23:5347-5356, 2005

22. Witzig T, Geyer S, Ghobrial I, et al: Anti-tumor activity of single-agent CCI-779 for relapsed mantle cell lymphoma: A phase II trial in the North Central Cancer Treatment Group. Blood 104, 2004 (abstr 129)

23. Atkins MB, Hidalgo M, Stadler WM, et al: Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol 22:909-918, 2004

24. Chan S, Scheulen ME, Johnston S, et al: Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. J Clin Oncol 23:5314-5322, 2005

25. Ansell SM, Geyer SM, Kurtin PJ, et al: Anti-tumor activity of mTOR inhibitor temsirolimus for relapsed mantle cell lymphoma: A phase II trial in North Central Cancer Treatment Group. J Clin Oncol 24:430s, 2006 (suppl; abstr 7532)

26. BCCA protocol summary for lymphoma palliative chemotherapy, revised September 1, 2008. http://www.bccancer.bc.ca/NR/rdonlyres/30FDD508-96AC-4555-B682-294EA3635B06/30217/LYPALL_Protocol_1Sep08.pdf

27. Tobinai K, Watanabe T, Ogura M, et al: Phase II study of oral fludarabine phosphate in relapsed indolent B-cell non-Hodgkin's lymphoma. J Clin Oncol 24:174-180, 2006

28. GlaxoSmithKline: Leukeran (chlorambucil) product insert. Research Triangle Park, NC, GlaxoSmithKline, 2006

29. Inwards DJ, Fishkin PAS, Hillman DW, et al: Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 113:108-116, 2008

30. Smith SM, Grinblatt D, Johnson JL, et al: Thalidomide has limited single-agent activity in relapsed or refractory indolent non-Hodgkin lymphomas: A phase II trial of the Cancer and Leukemia Group B. Br J Haematol 140:313-319, 2008

31. Bedford Laboratories: Vinblastine product insert. Bedford, OH, Bedford Laboratories, 2001

32. Bayer HealthCare Pharmaceuticals: Campath (alemtuzumab) product insert. Wayne, NJ, Bayer HealthCare Pharmaceuticals, 2007

33. Witzig TE, Vose JM, Kaplan HP, et al: Early results from a phase II study of lenalidomide monotherapy in relapsed/refractory indolent non-Hodgkin's lymphoma. Blood 108, 2006 (abstr 2482)

34. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244-1253, 1999

35. United States Food and Drug Administration: Guidance for industry clinical trial endpoints for the approval of cancer drugs and biologics. May 2007: 17. http://www.fda.gov/cber/gdlns/clintrialend.pdf

36. Smith SM, Pro B, Cisneros A, et al: Activity of single agent temsirolimus (CCI-779) in non-mantle cell non-Hodgkin lymphoma subtypes. J Clin Oncol 26:457s, 2008 (suppl; abstr 8514)

37. Foran JM, Rohatiner AZS, Cunningham D, et al: European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle cell lymphoma and previously treated mantle cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 18:317-324, 2000

38. Fisher RI, Bernstein SH, Kahl BS, et al: Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 24:4867-4874, 2006

39. Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271-2281, 2007

