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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Torisel® / Temsirolimus

PROTOCOL NO.: 3066K1-305-WW (B1771099)

PROTOCOL TITLE: An Open-Label, Randomized, Phase 3 Trial of Intravenous Temsirolimus (CCI-779) at Two Dose Levels Compared to Investigator's Choice Therapy in Relapsed, Refractory Subjects With Mantle Cell Lymphoma (MCL)

Study Centers: A total of 113 centers took part in the study and 64 centers enrolled subjects; 19 in the United States (US), 8 in Canada, 6 in France, 5 each in China and Spain, 4 in Italy, 3 each in Belgium, Germany, and the United Kingdom (UK), 2 each in Argentina and Sweden, and 1 each in Australia, Poland, the Netherlands, and Switzerland.

Study Initiation, Primary Completion, and Final Completion Dates:

Study Initiation Date: 23 May 2005

Primary Completion Date: 29 August 2007 (final data collection date for primary outcome measure)

Final Completion Date: 04 January 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To evaluate (independently assessed) progression-free survival (PFS).

Secondary Objectives: To evaluate safety and efficacy using the following endpoints and analyses:

- Safety and tolerability;
- Objective response rate ([ORR]: complete response [CR] + complete response unconfirmed [Cru] + partial response [PR]);
- Overall survival (OS).

METHODS:

Study Design: This was a controlled, randomized, open-label, multicenter, outpatient study comparing 2 different dosing regimens of temsirolimus with an Investigator's choice of therapy in subjects with relapsed/refractory MCL.

Subjects were to be randomly assigned in a 1:1:1 ratio to receive intravenous (IV) temsirolimus 175 mg (3 successive weekly doses) followed by 75 mg weekly, IV temsirolimus 175 mg (3 successive weekly doses) followed by 25 mg weekly, or the Investigator's choice of single-agent treatment.

The study consisted of a treatment period and follow-up periods for disease assessment and survival. During the treatment period, subjects were required to visit the clinic weekly for test article administration and safety assessments. Subjects were allowed to continue treatment until disease progression or unacceptable toxicity. Subjects who discontinued treatment without having disease progression or starting another anticancer therapy were followed for progression every 8 weeks during the first year, every 12 weeks during the second year, and every 6 months during years 3 to 5. Once subjects either had disease progression or began receiving another anticancer therapy, they entered long-term follow-up and were followed for survival every 3 months for up to 5 years. Disease progression status, anticancer therapies received, and serious adverse events (SAEs) considered to be related to temsirolimus were also recorded during long-term follow-up.

At the time of interim analysis, 25 subjects remained on treatment: 12 (22%) in the temsirolimus 175/75 mg group, 11 (20%) in the temsirolimus 175/25 mg group, and 2 (4%) in the Investigator's choice group. At that time, an amendment to the protocol was issued. Per this amendment, subjects who were still on treatment continued receiving treatment until disease progression or unacceptable toxicity. In addition, subjects receiving Investigator's choice therapy and subjects receiving temsirolimus 175/25 mg could crossover to receive treatment with temsirolimus 175/75 mg. Additionally, subjects who had discontinued Investigator's choice therapy for any reason and those subjects who had discontinued temsirolimus 175/25 mg for any reason and who were able to tolerate the 25 mg dose, could be eligible to crossover to temsirolimus 175/75 mg treatment.

During the additional period of observation following the end of data collection for the interim analysis, subjects who were still on treatment continued receiving treatment and visiting the clinic weekly to receive temsirolimus. After treatment discontinuation, subjects were contacted only once approximately 6 months after the last dose; every SAE considered to be related to temsirolimus was recorded.

The schedule of activities for the study is presented in Table 1 and Table 2.

Table 1. Schedule of Activities for Year 1: Week -4 to Week 52

	Screening/Baseline	Year 1 Treatment Period[a]											
Procedures	**Week –4 to 0**	**Week -2 to 0**	**W1[b]**	**W2**	**W3**	**W4**	**W5[c]**	**W6**	**W7**	**W8[d]**	**End of Tx**	**Disease Follow-Up**	**Long-Term Follow-Up**
Visit Window (Days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+14-49 Post Tx[e]**		
Informed consent	X												
Inclusion/exclusion criteria	X												
Demography	X												
Medical and disease history	X												
Pathology confirmation (tumor biopsy)[f]	X												
Vital signs		X	X				X				X		
Physical examination B-symptom evaluation[g]		X	X				X				X		
Serum pregnancy test		X[h]									X		
CBC with 5-part differential[i]		X	X	X	X	X	X	X	X	X	X		
Chemistry		X[j]	X				X				X		
Cholesterol, triglycerides		X[j]	X				X				X		
Direct bilirubin[k]		X	X				X				X		
KPS		X	X								X		
Coagulation test[l]		X											
ECG[m]		X	X								X		
Chest X ray[n]	X										X		
Disease assessment and CT scan (neck, chest, abdomen, pelvis)	X									X	X[e]	X[o]	
Temsirolimus administration[p]			----------X----------										
Investigator's choice therapy[q]			----------X----------										
Survival status													X[r]
Bone marrow aspirate and biopsy (unilateral or bilateral)	X									X[s]			
Adverse events	----------X----------												
Concomitant treatment	----------X----------												
Conclusion of treatment period											X[t]		
Conclusion of subject participation													X[u]

Table 1. Schedule of Activities for Year 1: Week -4 to Week 52

CBC = complete blood count; CPE = clinical planned event; CR = complete response; CRu = complete response unconfirmed; CT = computed tomography; ECG = electrocardiogram; KPS = Karnosfsky Performance Status; MCL = mantle cell lymphoma; PK = pharmacokinetic; PR = partial response; Tx = treatment; ULN = upper limit of normal; W = week.

a. Treatment period was defined as from the first dose of temsirolimus or Investigator's choice therapy to the last dose (ie, no further dosing).
b. Procedures at 8-week intervals, except ECG, PK, pharmacodynamic procedures, (Week 9, 17, 25, 33, 41, 49) unless otherwise indicated.
c. Procedures at 4-week intervals (Week 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49) unless otherwise indicated.
d. Procedures at 8-week intervals (Week 8, 16, 24, 32, 40, 48) unless otherwise indicated.
e. End of treatment visit completed approximately 4 weeks (Day 14-49) after last dose of either temsirolimus or Investigator's choice therapy. Disease assessment was performed for subjects who discontinued treatment if no assessment performed within previous 4 weeks of the visit. If end of treatment was within 4 weeks of the first dose then disease assessments was performed for all subjects who discontinued treatment.
f. Histopathology, immunophenotyping, cyclin D1 and 11, 14 chromosomal translocation analysis was performed at a central laboratory to confirm MCL diagnosis using a tumor biopsy sample.
g. B-symptom evaluation included
   - unexplained weight loss of >10% of the body weight during the 6 months before staging investigation
   - unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month
   - recurrent drenching night sweats during the previous month
h. Serum pregnancy test had to be performed within 1 week of randomization to either temsirolimus or the Investigator's choice treatment and whenever clinically indicated for women of childbearing potential.
i. CBC performed weekly. Included white blood cell count with 5-part differential, platelet count, red blood cell count, hemoglobin, and hematocrit.
j. Fasting sample required at screening only.
k. Required only if total bilirubin >1.5 x ULN.
l. Performed for subjects receiving anticoagulants at screening and as clinically indicated.
m. ECG performed in triplicate at the following time points for subjects receiving temsirolimus: screening/baseline, immediately after antihistamine pretreatment (Week 1, Day 1), immediately before end of infusion (Week 1, Day 1), 3 months after the first dose immediately before end of infusion, and at end of treatment. For subjects receiving Investigator's choice, time points were screening/baseline, immediately before treatment (Week 1, Day1) , approximately 30 minutes after starting treatment (Week 1, Day 1), 3 months after starting the first dose (approximately 30 minutes after dose), and at end of treatment.
n. Additional chest X-rays were performed whenever clinically indicated.
o. Disease assessment was also performed at follow-up visit. To confirm tumor response, CT scan of the neck, chest, abdomen, and pelvis were repeated after at least 4 weeks for subjects with CR/CRu/PR.
p. For subjects in either temsirolimus group, temsirolimus was administered on Day 1 of each week during the treatment period. The 175 mg starting dose was administered once weekly during Weeks 1, 2, and 3.
q. Subjects in the Investigator's choice group received treatment as per Investigator's discretion. Day 1 was defined as the first day of treatment (ie, first dose of medication chosen by the Investigator).
r. Progression status and survival could be captured via telephone.
s. Performed only if necessary to validate complete response.
t. Complete at end of treatment.
u. Complete at end of subject participation or death.

Table 2. Schedule of Activities for Year 2: Week 53 to Week 104

	Year 2 Treatment Period														
Procedures	**W 53**	**W 54**	**W 55**	**W 56**	**W 57**	**W 58**	**W 59**	**W 60[a]**	**W 61**	**W 62**	**W 63**	**W 64**	**End of Tx**	**Disease Follow-Up**	**Long-Term Follow-Up**
Visit Window (Days)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+14-49 Post Tx[b]**		
Vital signs								X					X		
Physical examination B-symptom evaluation[c]								X					X		
Serum pregnancy test													X		
CBC with 5-part differential[d]		X		X		X		X		X		X	X		
Chemistry								X					X		
Cholesterol, triglycerides								X					X		
Direct bilirubin[e]								X					X		
KPS								X					X		
Coagulation test[f]															
ECG													X		
Chest X-ray[g]													X		
Disease assessment and CT scan (neck, chest, abdomen, pelvis)								X					X[b]	X[h]	
Temsirolimus administration[i]	----------X----------														
Investigator's choice therapy[j]	----------X----------														
Survival status															X[k]
Bone marrow aspirate and biopsy (unilateral or bilateral)								X[l]							
Adverse events	----------X----------														
Concomitant treatment	----------X----------														
Conclusion of treatment period													X[m]		
Conclusion of subject participation															X[n]

CBC = complete blood count; CR = complete response; CRu = complete response unconfirmed; CT = computed tomography; ECG = electrocardiogram; KPS = Karnosfsky Performance Status; PR = partial response; Tx = treatment; ULN = upper limit of normal; W = week.

a. Procedures every 12 weeks during treatment period of second year (Week 60, 72, 84, 96).

Table 2. Schedule of Activities for Year 2: Week 53 to Week 104

b. End of treatment visit completed approximately 4 weeks (Day 14-49) after last dose of either temsirolimus or Investigator's choice therapy. Disease assessments were performed for subjects who discontinued treatment if no assessment had been performed within 12 weeks before the visit. ECG performed at end of treatment.

c. B-symptom evaluation included:

- unexplained weight loss of >10% of the body weight during the 6 months before staging investigation.
- unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month.
- recurrent drenching night sweats during the previous month.

d. CBC was performed every 2 weeks.

e. Required only if total bilirubin >1.5 x ULN.

f. Performed for subjects receiving anticoagulants as clinically indicated.

g. Additional chest X-rays performed whenever clinically indicated.

h. Disease assessment was also performed at follow-up visits. Tumor response was confirmed by repeating CT scan of the neck, chest, abdomen, and pelvis after at least 4 weeks for subjects in CR/CRu/PR.

i. For subjects in either temsirolimus group, temsirolimus was administered on Day 1 of each week during the treatment period.

j. For subjects in the Investigator's choice group, subjects received treatment as per Investigator's discretion.

k. Progression status and survival could be captured via telephone.

l. Performed only if necessary to validate CR.

m. Completed at end of treatment.

n. Completed at end of subject participation or death.

Number of Subjects (Planned and Analyzed): A total of 177 subjects were planned for enrollment into the study. A total of 169 subjects were randomly assigned to the 3 treatment groups in the study, 57 subjects in the temsirolimus 175/75 mg group, 56 in the 175/25 mg group, and 56 in the Investigator's choice group.

Of the 169 randomized subjects, 168 received study treatment; 38 in the US, 24 in France, 22 in Canada, 16 in Belgium, 13 in Germany, 11 in China, 10 in Italy, 9 each in Spain, and Sweden, 7 in the UK, 2 each in Argentina, Australia, the Netherlands, and Poland, and 1 in Switzerland.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for the study were male and female subjects aged 18 years and older who:

- Were diagnosed with MCL confirmed with histology, immunophenotype, and cyclin D1 analysis;
- Had received 2 to 7 prior therapies which may have included hematopoietic stem cell transplant (ie, induction + consolidation + maintenance);
- Had received prior treatment with an alkylating agent and an anthracycline, rituximab, individually or in combination, with a status that was at least 1 of the following:
  - Primary disease refractory to at least 2 regimens;
  - Refractory to at least 1 regimen after first relapse;
  - Refractory or untreated after second or greater relapse OR;
  - Disease refractory to first line and relapsed after second line. Chemotherapy combinations may have included, but were not limited to: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), FCM (fludarabine, cyclophosphamide, mitoxantrone), R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone), ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cisplatin, cytarabine) and hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone).

Subjects who were ≤6 months from allogeneic hematopoietic stem cell transplant and who were on immunosuppressive therapy or had evidence of graft versus host disease, subjects with prior Investigational therapy (defined as treatment that was not approved for any indication) within 3 weeks of first dose, and subjects with active central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, requirement for corticosteroids and/or progressive growth, (treated CNS metastases had to be stable for >2 weeks prior to Day 1) were excluded from the study.

Study Treatment: Temsirolimus was supplied as concentrate for injection in sterile 25 mg/mL vials.

Temsirolimus was administered as an IV infusion over 30 minutes. Before temsirolimus administration, results of complete blood count with differential and other tests as clinically indicated were reviewed. Subjects received premedication with 25 to 50 mg IV diphenhydramine (or similar antihistamine) approximately 30 minutes before the start of each temsirolimus infusion.

Subjects who were randomly assigned to either temsirolimus group received temsirolimus 175 mg administered IV once weekly for the first 3 weeks of treatment followed by either temsirolimus 25 mg or 75 mg IV once weekly. Subjects were to receive temsirolimus on the same day of the week throughout the treatment period; however, temsirolimus could be administered up to 2 days earlier or later, as long as AEs did not preclude administration at that time.

Subjects who were randomly assigned to the Investigator's choice group could receive 1 of the following single-agent treatments, as chosen by the Investigator:

- Fludarabine 25 mg/m^2 IV over 30 minutes daily for 5 consecutive days every 28 days or oral administration, as appropriate;
- Chlorambucil 0.1 (0.1-0.2) mg/kg orally (PO) daily for 3 to 6 weeks as required or 0.4 (0.3-0.8) mg/kg PO every 21 to 28 days;
- Gemcitabine 1 g/m^2 IV over 30 minutes on Days 1, 8, and 15 every 28 days or Day 1 and Day 8 every 21 days;
- Cyclophosphamide 300 (200-450) mg/m^2 PO daily for 5 consecutive days every 21 to 28 days, or 600 (400-1200) mg/m^2 IV every 21 to 28 days;
- Cladribine 5 mg/m^2 IV daily for 5 consecutive days every 28 days for 2-6 cycles depending on response;
- Etoposide 50 (50-150) mg/m^2 IV daily for 3-5 days every 21 to 28 days or 100 (50-300) mg/m^2 PO daily for 3-5 days every 21 to 28 days;
- Prednisone 40 (20-60) mg/m^2 PO daily or every other day;
- Dexamethasone 20 (20-40) mg PO/IV daily for 5 consecutive days every 14 to 28 days;

Investigators who wanted to use an agent, dose, or schedule other than those specified above were required to obtain approval from the Sponsor before the first dose. Combinations of 2 or more drugs approved for any indication were not permitted.

Efficacy and Safety Endpoints:

Efficacy Endpoints: The primary efficacy endpoint was PFS (independently assessed) and secondary efficacy endpoints were ORR (CR + CRu + PR) and OS.

Safety Endpoints: Overall safety and tolerability of prolonged drug administration.

Safety Evaluations: Safety was assessed by recording of AEs, physical examination (weight, vital signs and clinical documentation of observations related to AEs), and routine laboratory tests. Additional evaluations to assess treatment-emergent AEs (TEAEs) and SAEs and to document the reasons for delays, dose reduction, or interruption of treatment was performed as needed. AEs were graded according to the National Cancer Institute Common Terminology Criteria version 3.0.

Statistical Methods:

Intent-To-Treat (ITT) Population: All subjects who were randomized were included in the ITT population.

Evaluable Population: All randomized subjects who received at least 1 dose of test article and remained in the treatment phase of the study (time from randomization to the conclusion of treatment participation) for at least 8 weeks (except for early discontinuation due to disease progression or death), had no major protocol violations that could have confounded the effects of treatment, and had at least 1 screening tumor assessment and at least 1 post-baseline independent tumor assessment to which an overall response could be assigned.

Safety Population: All subjects who received at least 1 dose of a test article (either temsirolimus or Investigator's choice).

The primary and secondary efficacy analyses were performed using both the ITT and evaluable populations. The analysis based on the ITT population was the primary analysis. Safety analyses were performed using the safety population.

Statistical Methods: Summary statistics were provided for continuous variables. Percentages were provided for categorical variables.

To detect a hazard ratio (HR) of 2.07 (107% improvement in PFS with a median of 3.0 months for the Investigator's choice versus 6.2 months for temsirolimus groups, and with 80% power using a 2-sided log rank test at the 2.5% significance level), a total of 105 independently assessed events (progression or death) had to be observed. The primary efficacy analysis was conducted once 105 events were observed. Efficacy was to be declared if a statistically significant ($p<0.025$) difference in PFS distribution comparing either temsirolimus group with the Investigator's choice group was observed.

PFS was analyzed using the (unstratified) log-rank test and the survival function was estimated using the Kaplan-Meier method. For PFS and all time-to-event endpoints, subjects without an event on or before the data cutoff date were right-censored at the data cutoff date. Cox proportional hazard models were used to estimate the relative hazards of PFS for subjects in the temsirolimus groups versus the Investigator's choice group. The corresponding 97.5% confidence intervals (CIs) were calculated for Independent PFS, and 95% CIs were calculated for other PFS analyses.

ORR was analyzed separately using the Independent and Investigator tumor assessments. The observed rates and the associated 95% CIs for each treatment group were calculated.

The Fisher exact test was used to compare ORR in each temsirolimus group with ORR in the Investigator's choice group.

OS was analyzed using the same methods described for the primary PFS analysis.

RESULTS:

Subject Disposition and Demography: A total of 169 subjects were randomly assigned to the 3 treatment groups in the study (ITT population). There were 57 subjects in the temsirolimus 175/75 mg group, 56 subjects in the 175/25 mg group, and 56 subjects in the Investigator's choice group.

Of the 169 subjects in the ITT population, 168 entered the treatment phase of the study and received at least 1 dose of test article (57 subjects in the temsirolimus 175/75 mg group, 56 subjects in the temsirolimus 175/25 mg group, and 55 subjects in the Investigator's choice group. These subjects were evaluable for safety and constituted the safety population.

Table 3 presents summary of subject disposition.

Table 3. Subject Disposition (ITT Population)

Population	TEMSR 175/75 mg	TEMSR 175/25 mg	INV CHOICE	TEMSR 175/25 mg Then TEMSR 175/75 mg	INV CHOICE Then TEMSR 175/75 mg
Period 1[a]					
Screened=190					
Intent-to-treat (total randomized)	57	56	56	0	0
Treated	57	56	54	0	0
Total discontinued[b]	57 (100)	53 (94.6)	52 (92.9)	0	0
Death	40 (70.2)	41 (73.2)	37 (66.1)	0	0
Lost to follow-up	0	2 (3.6)	2 (3.6)	0	0
Other	15 (26.3)	9 (16.1)	9 (16.1)	0	0
Subject request	2 (3.5)	1 (1.8)	4 (7.1)	0	0
Period 2[a]					
Screened=7					
Intent-to-treat (total randomized)	0	0	0	3	4
Treated	0	0	0	3	4
Total discontinued[b]	0	0	0	3 (100)	4 (100)
Death	0	0	0	1 (33.3)	2 (50)
Other	0	0	0	1 (33.3)	2 (50)
Subject request	0	0	0	1 (33.3)	0

Treatment cross over was implemented as per Protocol amendment.
INV = Investigator's; ITT = intent to treat; N = number of subjects; TEMSR = temsirolimus.
a. Period 1: prior to treatment cross over, Period 2: after treatment cross over.
b. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 4 presents summary of subject populations by treatment groups.

Table 4. Summary of Subject Populations by Treatment Group

	TEMSR 175/75 mg (N=57)	TEMSR 175/25 mg (N=56)	INV CHOICE (N=56)	Total (N=169)
ITT population	57 (100.0)	56 (100.0)	56 (100.0)	169 (100.0)
Safety population	57 (100.0)	56 (100.0)	55 (98.2)[a]	168 (99.4)
Evaluable population[b]	28 (49.1)	30 (53.6)	28 (50.0)	86 (50.9)

INV = Investigator's; ITT = intent to treat; N = number of subjects; TEMSR = temsirolimus.

a. One subject is included in this number despite having crossed over to receive TEMSR before receiving any Investigator's choice treatment. Another subject is not included in this number because this subject, while randomized to the Investigator's choice group, did not receive any study treatment.

b. Were in the treatment phase for at least 8 weeks (or discontinued early because of disease progression or death) and had no major protocol violations.

A summary of demographic characteristics and baseline characteristics is presented in Table 5.

Table 5. Demographic and Baseline Characteristics (ITT Population)

Characteristic	TEMSR 175/75 mg (N=57)	TEMSR 175/25 mg (N=56)	INV CHOICE (N=56)	Total (N=169)
Age (years)				
N	57	56	56	169
Mean	66.5	67.8	62.9	65.7
Standard deviation	8.8	7.8	10.6	9.3
Minimum	44.0	43.0	39.0	39.0
Maximum	87.0	85.0	88.0	88.0
Median	67.0	68.5	64.5	67.0
Age category				
Age <65	24 (42.1)	17 (30.4)	28 (50.0)	69 (40.8)
Age ≥65	33 (57.9)	39 (69.6)	28 (50.0)	100 (59.2)
Gender (n, %)				
Female	9 (15.8)	15 (26.8)	8 (14.3)	32 (18.9)
Male	48 (84.2)	41 (73.2)	48 (85.7)	137 (81.1)
Race (n, %)				
Asian	4 (7.0)	4 (7.1)	6 (10.7)	14 (8.3)
Black or African American	1 (1.8)	0	0	1 (0.6)
Other	1 (1.8)	1 (1.8)	1 (1.8)	3 (1.8)
White	51 (89.5)	51 (91.1)	49 (87.5)	151 (89.3)
Height (cm)				
N	56	56	55	167
Mean	171.3	170.7	172.4	171.5
Standard deviation	8.6	9.5	8.6	8.9
Minimum	154.5	148.0	146.5	146.5
Maximum	189.0	191.0	188.0	191.0
Median	168.5	170.2	173.3	171.0
Missing	1	0	1	2
Weight (kg)				
N	57	55	56	168
Mean	73.6	72.6	79.3	75.2
Standard deviation	13.7	13.5	17.9	15.4
Minimum	47.8	47.0	38.5	38.5
Maximum	116.4	105.3	123.4	123.4
Median	73.1	74.5	75.0	74.0
Missing	0	1	0	1
Karnofsky score (n, %)				
60-70	11 (19.3)	8 (14.3)	6 (10.7)	25 (14.8)
80-90	31 (54.4)	31 (55.4)	34 (60.7)	96 (56.8)
100	15 (26.3)	17 (30.4)	16 (28.6)	48 (28.4)

Other race includes Hispanic, North African, Greek.
INV = Investigator's; ITT = intent to treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; TEMSR = temsirolimus.

Efficacy Results: Efficacy analyses were performed once 105 PFS events based on the independent assessment of disease progression or death had been observed. The efficacy analyses presented below are based on data collected until the field data cut-off date (19 July 2007) for the interim analysis. Following the interim analysis and protocol amendment, efficacy data were no longer collected.

PFS: The results of the PFS analysis for the ITT population are summarized in Table 6.

As of 19 July 2007, 29 subjects in the temsirolimus 175/75 mg group, 38 subjects in the temsirolimus 175/25 mg group, and 38 subjects in the Investigator's choice group had PFS events based on the Independent assessment. Temsirolimus 175/75 mg led to an

improvement in PFS of 127% compared with Investigator's choice, which was statistically significant (HR=0.44; log-rank p-value=0.0009). Temsirolimus 175/25 mg led to an improvement in PFS of 54% compared with Investigator's choice, but the difference was not statistically significant (HR=0.65; log-rank p-value=0.0618).

Based on the Investigator assessment of PFS, both temsirolimus groups showed statistically significant improvements in PFS compared with Investigator's choice.

Table 6. Progression-Free Survival (ITT Population)

	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Independent assessment[a]			
Number of subjects with PD or who died (n, %)	29 (53.8)	38 (70.4)	38 (70.4)
Number of censored subjects (n, %)	25 (46.2)	16 (29.6)	16 (29.6)
Median PFS in months (97.5% CI)	4.8 (3.1, 8.1)	3.4 (1.9, 5.5)	1.9 (1.6, 2.5)
% change in median PFS from INV CHOICE	153%	79%	
Hazard ratio[b] (97.5% CI)	0.44 (0.25, 0.78)	0.65 (0.39, 1.10)	
p-value[c]	0.0009	0.0618	
Investigators' assessment[d]			
Number of subjects with PD or who died (n, %)	35 (64.8)	38 (70.4)	45 (83.4)
Number of censored subjects (n, %)	19 (35.2)	16 (29.6)	9 (16.6)
Median PFS in months (95% CI)	4.8 (2.9, 7.0)	3.7 (3.4, 6.2)	1.8 (1.6, 2.0)
% change in median PFS from INV CHOICE	167%	106%	
Hazard ratio[b] (95% CI)	0.39 (0.25, 0.63)	0.41 (0.26, 0.65)	
p-value[c]	<0.0001	<0.0001	

CI = confidence interval; INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; PD = progressive disease; PFS = progression-free survival; TEMSR = temsirolimus.

a. Disease assessment was based on radiographic review by Independent Radiologists and review of clinical data by Independent Oncologists.
b. Compared with INV CHOICE based on Cox proportional hazard model.
c. Compared with INV CHOICE based on log-rank test.
d. Disease assessment was based on review of radiographic and clinical data by the Investigator.

ORR: A summary of best overall response is provided in Table 7.

Table 7. Best Overall Response (ITT Population)

	TEMSR 175/75 mg (N=54) n (%)	TEMSR 175/25 mg (N=54) n (%)	INV CHOICE (N=54) n (%)
Independent assessment[a]			
Assessment not available[b]	14 (25.9)	11 (20.4)	14 (25.9)
CR	1 (1.9)	0	1 (1.9)
PR	11 (20.4)	3 (5.6)	0
SD[c]	16 (29.6)	17 (31.5)	11 (20.4)
PD	12 (22.2)	23 (42.6)	28 (51.9)
Investigator assessment[d]			
Assessment not available[e]	17 (31.5)	15 (27.8)	7 (13.0)
CR	2 (3.7)	1 (1.9)	0
PR	5 (9.3)	7 (13.0)	1 (1.9)
SD[c]	19 (35.2)	18 (33.3)	16 (29.6)
PD	11 (20.4)	13 (24.1)	30 (55.6)

Best overall response was determined at each time point for the Independent assessment and only at the end-of-treatment visit for the Investigator assessment.
CR = complete response; INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; PD = progressive disease; PR = partial response; SD = stable disease; TEMSR = temsirolimus.

a. Disease assessment was based on radiographic review by Independent Radiologists and review of clinical data by Independent Oncologists.
b. Independent assessments were not available in cases where assessment were not of the quality required for reading by the Independent reviewer, were missing, or were not yet read by the Independent reviewer.
c. Must have met the SD criteria at least once after randomization at a minimum of 8 weeks (2-week window).
d. Disease assessment was based on review of radiographic and clinical data by the Investigator.
e. Investigator assessments of best overall response were not available for subjects who came off study without having an end-of-treatment visit or who had not had an end-of-treatment visit before the data cutoff date.

ORR in the ITT population is summarized in Table 8.

As per Independent assessment, ORR in the temsirolimus 175/75 mg group was significantly higher than that in the Investigator's choice group (p-value=0.0019), but ORR in the temsirolimus 175/25 mg group was not (p-value=0.6179).

As per Investigator assessment, the difference between the ORR in the temsirolimus 175/75 mg and Investigator's choice group was not statistically significant (p-value=0.0602), but the difference between the ORR in the temsirolimus 175/25 mg group and that in the Investigator's choice group was significant (p-value=0.0314).

Table 8. Objective Response Rate (ITT Population)

	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Independent assessment[a]			
Number of subjects with CR, CRu or PR (n, %)	12 (22.2)	3 (5.6)	1 (1.9)
95% CI for rate	(11.1, 33.3)	(0.0, 11.7)	(0.0, 5.4)
p-value[b]	0.0019	0.6179	-
Number of subjects with CR (n, %)	1 (1.9)	0 (0.0)	1 (1.9)
95% CI for rate	(0.0, 5.4)	(0.0, 0.0)	(0.0, 5.4)
p-value[b]	1.0000	1.0000	-
Investigator's assessment[c]			
Number of subjects with CR, Cru or PR (n, %)	7 (13.0)	8 (14.8)	1 (1.9)
95% CI for rate	(4.0, 21.9)	(5.3, 24.3)	(0.0, 5.4)
p-value[b]	0.0602	0.0314	-
Number of subjects with CR (n, %)	2 (3.7)	1 (1.9)	0 (0.0)
95% CI for rate	(0.0, 8.7)	(0.0, 5.4)	(0.0, 0.0)
p-value[b]	0.4953	1.0000	-

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; PR = partial response; TEMSR = temsirolimus.

a. Disease assessment was based on radiographic review by Independent Radiologists and review of clinical data by Independent Oncologists.
b. Compared with INV CHOICE alone based on the Fisher exact test.
c. Disease assessment was based on review of radiographic and clinical data by the Investigator.

OS: The results of the OS analysis for the ITT population are summarized in Table 9.

Table 9. Overall Survival (ITT Population)

	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Number of deaths (n, %)	29 (53.8)	31 (57.4)	31 (57.4)
Median OS in months (95% CI)	11.1 (8.2, 18.0)	8.8 (6.4, 14.5)	9.5 (5.3, 15.1)
Hazard ratio[a] (95% CI)	0.77 (0.46, 1.28)	0.98 (0.60, 1.62)	
p-value[b]	0.3053	0.9515	

CI = confidence interval; INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; OS = overall survival; TEMSR = temsirolimus.

a. Compared with INV CHOICE based on Cox proportional hazard model.
b. Compared with INV CHOICE based on log-rank test.

Safety Results: Safety results for the entire study period up to the time of last subject last visit are presented below.

A summary of TEAEs for the safety population is shown in Table 10.

Table 10. Summary of Adverse Events: Number (%) of Subjects-Safety Population (Before Crossover)

Parameter, n (%)	TEMSR 175/75 mg (N=57)	TEMSR 175/25 mg (N=56)	INV CHOICE (N=54)
Any treatment-emergent adverse event	57 (100.0)	56 (100.0)	52 (96.3)
Grade 3 or 4 treatment-emergent adverse events	54 (94.7)	49 (87.5)	41 (75.9)
Serious adverse events	34 (59.6)	34 (60.7)	15 (27.8)
Adverse events leading to discontinuation	18 (31.6)	11 (19.6)	6 (11.1)
Adverse events leading to dose reductions	38 (66.7)	27 (48.2)	7 (13.0)
Adverse events leading to dose delays	48 (84.2)	43 (76.8)	26 (48.1)
Deaths (ITT population) within 14 days of last dose	4 (7.0)	2 (3.6)	1 (1.9)

Adverse events and serious adverse events are not separated out.
Adverse events were coded with Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) 5th Edition with Sponsor internal modification.
All Adverse events that occurred (started) before the crossover date were considered.
INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria; TEMSR = temsirolimus.

Table 11 presents a summary of TEAEs that occurred during the crossover period.

Table 11. Brief Summary of Adverse Events: Number (%) of Subjects-Safety Population (Crossover Period)

Parameter, n (%)	TEMSR 175/75 mg (N=7)
Any treatment-emergent adverse events	7 (100.0)
Grade 3 or 4 treatment-emergent adverse events	6 (85.7)
Serious adverse events	2 (28.6)
Adverse events leading to discontinuation	1 (14.3)
Adverse events leading to dose reductions	5 (71.4)
Adverse events leading to dose delays	6 (85.7)
Deaths (ITT population) within 14 days of last dose	0

Adverse events and serious adverse events are not separated out.
Adverse events were coded with Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) 5th Edition with Sponsor internal modification.
All Adverse events that occurred (started) after the crossover date were considered.
INV = Investigator's; ITT = intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria; TEMSR = temsirolimus.

TEAEs: Table 12 presents TEAEs reported in ≥5% of subjects in any treatment group during the study.

The frequency of TEAEs in the Investigator's choice group was similar to or lower than that in the temsirolimus groups for most events. The exceptions, for which the AE frequency was higher in the Investigator's choice group, were constipation, leukopenia, lymphopenia, neutropenia, dyspnea, sweating, and edema.

The incidence of TEAEs was generally similar between the 2 temsirolimus groups, with the following exceptions for which the incidence in the temsirolimus 175/75 mg group was higher than in the temsirolimus 175/25 mg group: chills, mucositis, rectal hemorrhage, muscle cramp, anxiety, sinusitis, constipation, arthralgia, acne, erythema, taste perversion, and upper respiratory infection.

Table 12. Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in any Treatment Group-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3 n (%)	INV CHOICE Then TEMSR 175/75 mg N=4 n (%)
Any adverse event	57 (100)	56 (100)	52 (96.3)	3 (100)	4 (100)
Body as a whole	53 (93.0)	52 (92.9)	34 (63.0)	3 (100)	3 (75.0)
Abdominal pain	14 (24.6)	16 (28.6)	9 (16.7)	0	2 (50.0)
Accidental injury	4 (7.0)	6 (10.7)	1 (1.9)	0	0
Asthenia	38 (66.7)	34 (60.7)	13 (24.1)	3 (100)	1 (25.0)
Back pain	8 (14.0)	8 (14.3)	2 (3.7)	0	1 (25.0)
Cellulitis	1 (1.8)	2 (3.6)	2 (3.7)	0	1 (25.0)
Chest pain	6 (10.5)	4 (7.1)	2 (3.7)	0	0
Chills	14 (24.6)	5 (8.9)	6 (11.1)	0	0
Face edema	4 (7.0)	1 (1.8)	0	0	0
Fever	21 (36.8)	16 (28.6)	17 (31.5)	0	2 (50.0)
Flu syndrome	2 (3.5)	5 (8.9)	1 (1.9)	0	0
Headache	9 (15.8)	13 (23.2)	5 (9.3)	0	2 (50.0)
Hernia	0	0	0	0	1 (25.0)
Infection	17 (29.8)	15 (26.8)	3 (5.6)	0	2 (50.0)
Neoplasm	2 (3.5)	3 (5.4)	0	0	0
Non-specified drug reaction	3 (5.3)	1 (1.8)	0	0	0
Pain	19 (33.3)	13 (23.2)	2 (3.7)	1 (33.3)	2 (50.0)
Pelvic pain	0	3 (5.4)	1 (1.9)	0	0
Cardiovascular system	18 (31.6)	21 (37.5)	15 (27.8)	0	1 (25.0)
Hemorrhage	3 (5.3)	2 (3.6)	0	0	1 (25.0)
Hypertension	2 (3.5)	5 (8.9)	0	0	0
Hypotension	2 (3.5)	4 (7.1)	2 (3.7)	0	0
Tachycardia	5 (8.8)	4 (7.1)	2 (3.7)	0	0
Tachycardia sinus	1 (1.8)	3 (5.4)	0	0	0
Thrombophlebitis	0	3 (5.4)	0	0	0
Digestive system	50 (87.7)	42 (75.0)	26 (48.1)	2 (66.7)	3 (75.0)
Abdominal distension	1 (1.8)	0	0	0	1 (25.0)
Anorexia	23 (40.4)	17 (30.4)	8 (14.8)	1 (33.3)	0
Aphthous stomatitis	3 (5.3)	4 (7.1)	0	0	0
Blood in stool	1 (1.8)	3 (5.4)	0	0	0
Constipation	9 (15.8)	4 (7.1)	10 (18.5)	0	2 (50.0)
Diarrhea	26 (45.6)	19 (33.9)	6 (11.1)	1 (33.3)	0
Dry mouth	4 (7.0)	2 (3.6)	1 (1.9)	0	1 (25.0)
Dyspepsia	2 (3.5)	2 (3.6)	3 (5.6)	0	0
Dysphagia	6 (10.5)	3 (5.4)	0	0	0
Melena	3 (5.3)	0	1 (1.9)	0	0
Mouth pain	1 (1.8)	0	0	0	1 (25.0)
Mouth ulceration	3 (5.3)	5 (8.9)	0	0	0
Mucositis	21 (36.8)	9 (16.1)	0	1 (33.3)	2 (50.0)
Nausea	14 (24.6)	17 (30.4)	11 (20.4)	1 (33.3)	2 (50.0)
Rectal hemorrhage	5 (8.8)	1 (1.8)	1 (1.9)	0	0
Stomatitis	12 (21.1)	6 (10.7)	3 (5.6)	0	0
Vomiting	8 (14.0)	7 (12.5)	3 (5.6)	0	2 (50.0)
Hemic and lymphatic system	54 (94.7)	50 (89.3)	44 (81.5)	3 (100)	4 (100)
Anemia	31 (54.4)	30 (53.6)	24 (44.4)	1 (33.3)	3 (75.0)
Ecchymosis	4 (7.0)	4 (7.1)	2 (3.7)	0	0
Leukocytosis	3 (5.3)	3 (5.4)	1 (1.9)	0	0
Leukopenia	10 (17.5)	12 (21.4)	22 (40.7)	1 (33.3)	1 (25.0)
Lymphadenopathy	3 (5.3)	2 (3.6)	2 (3.7)	0	0

Table 12. Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in any Treatment Group-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3 n (%)	INV CHOICE Then TEMSR 175/75 mg N=4 n (%)
Lymphedema	3 (5.3)	0	0	0	0
Lymphocytosis	3 (5.3)	1 (1.8)	0	0	0
Lymphopenia	7 (12.3)	7 (12.5)	10 (18.5)	0	0
Neutropenia	15 (26.3)	19 (33.9)	22 (40.7)	2 (66.7)	1 (25.0)
Prothrombin time prolonged	0	0	0	1 (33.3)	0
Thrombocytopenia	45 (78.9)	47 (83.9)	29 (53.7)	3 (100)	4 (100)
Metabolic and nutritional	43 (75.4)	38 (67.9)	24 (44.4)	0	3 (75.0)
Creatinine increased	5 (8.8)	7 (12.5)	0	0	0
Dehydration	2 (3.5)	4 (7.1)	0	0	0
Edema	3 (5.3)	6 (10.7)	6 (11.1)	0	0
Gamma globulin decreased	3 (5.3)	1 (1.8)	0	0	0
Hypercholesteremia	11 (19.3)	10 (17.9)	0	0	0
Hyperglycemia	9 (15.8)	6 (10.7)	6 (11.1)	0	1 (25.0)
Hyperlipemia	7 (12.3)	11 (19.6)	0	0	1 (25.0)
Hypocalcemia	6 (10.5)	5 (8.9)	0	0	0
Hypokalemia	14 (24.6)	10 (17.9)	1 (1.9)	0	0
Hyponatremia	2 (3.5)	0	1 (1.9)	0	1 (25.0)
Hypophosphatemia	7 (12.3)	6 (10.7)	0	0	0
Hypoproteinemia	2 (3.5)	3 (5.4)	0	0	0
Lactic dehydrogenase increased	6 (10.5)	5 (8.9)	1 (1.9)	0	0
Peripheral edema	14 (24.6)	13 (23.2)	9 (16.7)	0	1 (25.0)
SGOT increased	2 (3.5)	6 (10.7)	1 (1.9)	0	0
SGPT increased	1 (1.8)	3 (5.4)	1 (1.9)	0	0
Weight gain	0	0	0	0	1 (25.0)
Weight loss	10 (17.5)	12 (21.4)	5 (9.3)	0	0
Musculoskeletal system	20 (35.1)	12 (21.4)	4 (7.4)	1 (33.3)	1 (25.0)
Arthralgia	12 (21.1)	5 (8.9)	1 (1.9)	0	0
Bone pain	1 (1.8)	3 (5.4)	0	1 (33.3)	1 (25.0)
Joint disorder	4 (7.0)	0	0	0	0
Leg cramps	3 (5.3)	3 (5.4)	1 (1.9)	0	0
Muscle cramp	7 (12.3)	2 (3.6)	1 (1.9)	0	0
Myalgia	5 (8.8)	3 (5.4)	1 (1.9)	0	0
Nervous system	30 (52.6)	27 (48.2)	15 (27.8)	1 (33.3)	1 (25.0)
Anxiety	9 (15.8)	4 (7.1)	3 (5.6)	0	0
Depression	5 (8.8)	5 (8.9)	0	0	0
Dizziness	4 (7.0)	6 (10.7)	1 (1.9)	0	0
Insomnia	12 (21.1)	6 (10.7)	4 (7.4)	0	0
Neuropathy	2 (3.5)	4 (7.1)	1 (1.9)	0	0
Paresthesia	4 (7.0)	6 (10.7)	3 (5.6)	1 (33.3)	0
Sleep disorder	0	0	0	0	1 (25.0)
Respiratory system	42 (73.7)	39 (69.6)	27 (50.0)	1 (33.3)	4 (100)
Bronchitis	4 (7.0)	3 (5.4)	3 (5.6)	0	0
Cough increased	19 (33.3)	18 (32.1)	5 (9.3)	0	0
Dyspnea	13 (22.8)	12 (21.4)	16 (29.6)	1 (33.3)	2 (50.0)
Epistaxis	26 (45.6)	16 (28.6)	3 (5.6)	1 (33.3)	2 (50.0)
Hypoxia	1 (1.8)	1 (1.8)	0	0	1 (25.0)
Pharyngitis	7 (12.3)	9 (16.1)	4 (7.4)	0	0
Pleural disorder	0	0	0	0	1 (25.0)
Pleural effusion	6 (10.5)	3 (5.4)	4 (7.4)	0	0
Pneumonia	6 (10.5)	8 (14.3)	5 (9.3)	0	1 (25.0)

Table 12. Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in any Treatment Group-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3 n (%)	INV CHOICE Then TEMSR 175/75 mg N=4 n (%)
Pulmonary physical finding	1 (1.8)	5 (8.9)	2 (3.7)	0	0
Rhinitis	6 (10.5)	5 (8.9)	3 (5.6)	0	0
Sinusitis	6 (10.5)	2 (3.6)	0	0	0
Upper respiratory infection	9 (15.8)	4 (7.1)	2 (3.7)	0	2 (50.0)
Voice alteration	3 (5.3)	1 (1.8)	0	0	0
Skin and appendages	40 (70.2)	36 (64.3)	23 (42.6)	2 (66.7)	1 (25.0)
Acne	5 (8.8)	2 (3.6)	0	0	0
Dry skin	7 (12.3)	5 (8.9)	1 (1.9)	0	0
Eczema	3 (5.3)	3 (5.4)	0	0	0
Erythema	6 (10.5)	1 (1.8)	2 (3.7)	1 (33.3)	0
Fungal dermatitis	1 (1.8)	3 (5.4)	0	1 (33.3)	0
Herpes simplex	6 (10.5)	10 (17.9)	4 (7.4)	0	1 (25.0)
Maculopapular rash	1 (1.8)	3 (5.4)	1 (1.9)	0	0
Nail disorder	11 (19.3)	10 (17.9)	1 (1.9)	0	0
Night sweats	5 (8.8)	3 (5.4)	4 (7.4)	0	0
Pruritic rash	5 (8.8)	0	0	0	0
Pruritus	16 (28.1)	12 (21.4)	3 (5.6)	1 (33.3)	1 (25.0)
Rash	21 (36.8)	19 (33.9)	6 (11.1)	0	0
Skin carcinoma	0	1 (1.8)	0	1 (33.3)	0
Skin disorder	3 (5.3)	3 (5.4)	0	0	0
Sweating	1 (1.8)	3 (5.4)	7 (13.0)	0	0
Special senses	23 (40.4)	15 (26.8)	5 (9.3)	1 (33.3)	1 (25.0)
Abnormal vision	3 (5.3)	0	0	0	0
Conjunctivitis	4 (7.0)	2 (3.6)	0	0	0
Diplopia	0	0	0	0	1 (25.0)
Eye disorder	3 (5.3)	0	0	0	0
Eye hemorrhage	3 (5.3)	1 (1.8)	0	0	0
Parosmia	3 (5.3)	0	1 (1.9)	0	0
Taste loss	5 (8.8)	3 (5.4)	0	1 (33.3)	0
Taste perversion	9 (15.8)	2 (3.6)	1 (1.9)	0	0
Urogenital system	17 (29.8)	15 (26.8)	6 (11.1)	0	1 (25.0)
Dysuria	4 (7.0)	5 (8.9)	1 (1.9)	0	0
Hematuria	1 (1.8)	1 (1.8)	0	0	1 (25.0)
Urinary frequency	4 (7.0)	1 (1.8)	0	0	0
Urinary tract infection	3 (5.3)	5 (8.9)	0	0	0
Adverse event associated with miscellaneous factors	3 (5.3)	4 (7.1)	2 (3.7)	1 (33.3)	0
Local reaction to procedure	3 (5.3)	3 (5.4)	1 (1.9)	1 (33.3)	0

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; INV = Investigator's; N = number of subjects; n = number of subjects with adverse events; nos = not otherwise specified; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject could report 2 or more different AEs in the same body system.

Severity of AEs: The percentage of subjects who experienced Grade 3/4 TEAEs was highest in the temsirolimus 175/75 mg group (94.7%) and lower in the temsirolimus 175/25 mg group (87.5%) and Investigator's choice group (74.1%). The following Grade 3/4 events were more frequent in the temsirolimus groups: asthenia, fever, infection, mucositis,

hyperglycemia, pneumonia, diarrhea, thrombocytopenia, hypokalemia, hypophosphatemia, lymphoma, pruritis, rash, and peripheral edema. Three Grade 3/4 events; leukopenia, lymphopenia, and neutropenia were more frequent in the Investigator's choice group. Otherwise, the frequency of individual Grade 3/4 events (preferred terms) was generally similar between groups.

The Grade 3/4 TEAEs that occurred during the crossover period were similar to those seen in the safety population before crossover.

SAEs: Table 13 presents treatment-emergent SAEs reported during the study.

SAEs with markedly higher frequency in the temsirolimus groups included fever, diarrhea, general physical health deterioration, and pneumonia. There were no body systems or preferred terms for which the frequency of SAEs was notably higher in the Investigator's choice group.

Table 13. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3	INV CHOICE Then TEMSR 175/75 mg N=4
Any adverse event	34 (59.6)	34 (60.7)	14 (25.9)	1 (33.3)	1 (25.0)
Body as a whole	18 (31.6)	16 (28.6)	7 (13.0)	0	1 (25.0)
Abdominal pain	1 (1.8)	0	0	0	0
Accidental injury	0	1 (1.8)	0	0	0
Asthenia	2 (3.5)	3 (5.4)	2 (3.7)	0	0
Back pain	0	2 (3.6)	0	0	0
Cellulitis	2 (3.5)	0	0	0	1 (25.0)
Chills	1 (1.8)	0	1 (1.9)	0	0
Fever	8 (14.0)	7 (12.5)	1 (1.9)	0	0
General physical health deterioration	3 (5.3)	3 (5.4)	1 (1.9)	0	0
Headache	1 (1.8)	0	0	0	0
Infection	3 (5.3)	2 (3.6)	2 (3.7)	0	1 (25.0)
Neutropenic fever	3 (5.3)	1 (1.8)	1 (1.9)	0	0
Sepsis	2 (3.5)	1 (1.8)	1 (1.9)	0	0
Septic shock	1 (1.8)	1 (1.8)	0	0	0
Cardiovascular system	2 (3.5)	3 (5.4)	4 (7.4)	0	0
Angina pectoris	1 (1.8)	0	0	0	0
Atrial flutter	0	1 (1.8)	0	0	0
Cerebrovascular accident	0	1 (1.8)	0	0	0
Endocarditis	0	0	1 (1.9)	0	0
Heart failure	0	0	1 (1.9)	0	0
Hypervolemia	0	0	1 (1.9)	0	0
Pulmonary embolus	0	0	1 (1.9)	0	0
Syncope	1 (1.8)	0	0	0	0
Tachycardia	0	1 (1.8)	0	0	0
Ventricular tachycardia	0	1 (1.8)	0	0	0
Digestive system	12 (21.1)	9 (16.1)	1 (1.9)	0	0
Anorexia	1 (1.8)	0	0	0	0
Diarrhea	4 (7.0)	4 (7.1)	0	0	0
Duodenal ulcer perforation	1 (1.8)	0	0	0	0
Enteritis	0	1 (1.8)	0	0	0
Gastritis	1 (1.8)	1 (1.8)	0	0	0
Gastroenteritis	0	1 (1.8)	0	0	0
Gastrointestinal hemorrhage	1 (1.8)	0	0	0	0
Liver function tests abnormal	1 (1.8)	0	0	0	0
Melena	1 (1.8)	0	1 (1.9)	0	0
Mouth ulceration	1 (1.8)	0	0	0	0
Rectal disorder	0	1 (1.8)	0	0	0
Rectal hemorrhage	1 (1.8)	0	0	0	0
Stomatitis	0	1 (1.8)	0	0	0
Ulcerative colitis	1 (1.8)	0	0	0	0
Hemic and lymphatic system	4 (7.0)	6 (10.7)	4 (7.4)	0	0
Acute lymphoblastic leukemia	0	0	1 (1.9)	0	0
Leukocytosis	2 (3.5)	0	0	0	0
Leukopenia	0	0	1 (1.9)	0	0
Lymphoma	1 (1.8)	2 (3.6)	1 (1.9)	0	0

Table 13. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3	INV CHOICE Then TEMSR 175/75 mg N=4
Neutropenia	1 (1.8)	0	2 (3.7)	0	0
Thrombocytopenia	0	4 (7.1)	0	0	0
Metabolic and nutritional	3 (5.3)	4 (7.1)	1 (1.9)	0	0
Creatinine increased	0	1 (1.8)	0	0	0
Dehydration	1 (1.8)	0	0	0	0
Edema	0	0	1 (1.9)	0	0
Hypoglycemia	0	1 (1.8)	0	0	0
Hypokalemia	2 (3.5)	1 (1.8)	0	0	0
Peripheral edema	0	1 (1.8)	0	0	0
Nervous system	2 (3.5)	1 (1.8)	0	0	0
Facial paralysis	1 (1.8)	0	0	0	0
Neuralgia	1 (1.8)	0	0	0	0
Somnolence	0	1 (1.8)	0	0	0
Respiratory system	17 (29.8)	14 (25.0)	5 (9.3)	1 (33.3)	1 (25.0)
Bronchitis	1 (1.8)	0	0	0	0
Carcinoma of lung	0	1 (1.8)	0	0	0
Cough increased	1 (1.8)	2 (3.6)	1 (1.9)	0	0
Dyspnea	0	2 (3.6)	0	0	0
Eosinophilic pneumonia	1 (1.8)	0	0	0	0
Epistaxis	2 (3.5)	1 (1.8)	0	0	0
Hyperventilation	1 (1.8)	0	0	0	0
Hypoxia	1 (1.8)	0	0	0	0
Interstitial pneumonia	1 (1.8)	0	0	0	0
Lung disorder	1 (1.8)	0	0	0	0
Lung edema	1 (1.8)	0	0	0	0
Lung fibrosis	1 (1.8)	0	0	0	0
Lung infiltration nos	1 (1.8)	2 (3.6)	0	0	0
Pleural effusion	0	1 (1.8)	1 (1.9)	1 (33.3)	0
Pleuritic pain	0	0	1 (1.9)	0	0
Pneumonia	6 (10.5)	4 (7.1)	2 (3.7)	0	1 (25.0)
Pneumonitis	1 (1.8)	3 (5.4)	0	0	0
Respiratory distress syndrome	1 (1.8)	0	0	0	0
Respiratory failure	1 (1.8)	2 (3.6)	0	0	0
Rhinitis	0	1 (1.8)	0	0	0
Skin and appendages	2 (3.5)	2 (3.6)	0	0	0
Acne	1 (1.8)	0	0	0	0
Fungal dermatitis	1 (1.8)	0	0	0	0
Herpes zoster	0	1 (1.8)	0	0	0
Rash	1 (1.8)	0	0	0	0
Skin carcinoma	0	1 (1.8)	0	0	0
Special senses	0	1 (1.8)	0	0	0
Conjunctivitis	0	1 (1.8)	0	0	0
Urogenital system	0	4 (7.1)	1 (1.9)	0	0
Acute kidney failure	0	1 (1.8)	0	0	0
Genital edema	0	0	1 (1.9)	0	0
Kidney function abnormal	0	2 (3.6)	0	0	0
Urinary retention	0	1 (1.8)	0	0	0

Table 13. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events-Safety Population

Body System[a] Adverse Event	Prior to Treatment Crossover			After Treatment Crossover	
	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)	TEMSR 175/25 mg Then TEMSR 175/75 mg N=3	INV CHOICE Then TEMSR 175/75 mg N=4

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) before the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; INV = Investigator's; N = number of subjects; n = number of subjects with adverse events; nos = not otherwise specified; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

Permanent Discontinuation From the Study Due to AEs: Discontinuations due to AEs are summarized in Table 14.

AEs leading to discontinuation in more than 1 subject in the Investigator's choice group were thrombocytopenia and pneumonia. AEs leading to discontinuation in more than 1 subject in the temsirolimus 175/75 mg group were asthenia and thrombocytopenia. The only AE leading to discontinuation in more than 1 subject in the temsirolimus 175/25 mg group was thrombocytopenia.

Table 14. Number (%) of Subjects Reporting Adverse Events Leading to Treatment Discontinuation-Safety Population

Body System[a] Adverse Event	TEMSR 175/75 mg N=57 n (%)	TEMSR 175/25 mg N=56 n (%)	INV CHOICE N=54 n (%)
Any adverse event	18 (31.6)	11 (19.6)	6 (11.1)
Body as a whole	4 (7.0)	3 (5.4)	0
Asthenia	4 (7.0)	0	0
Back pain	0	1 (1.8)	0
Infection	0	1 (1.8)	0
Septic shock	0	1 (1.8)	0
Digestive system	4 (7.0)	1 (1.8)	0
Colitis	1 (1.8)	0	0
Diarrhea	1 (1.8)	0	0
Liver function tests abnormal	1 (1.8)	0	0
Mucositis	0	1 (1.8)	0
Ulcerative colitis	1 (1.8)	0	0
Hemic and lymphatic system	5 (8.8)	3 (5.4)	4 (7.4)
Hemolytic anemia	0	0	1 (1.9)
Lymphocytosis	1 (1.8)	0	0
Neutropenia	0	0	1 (1.9)
Thrombocytopenia	4 (7.0)	3 (5.4)	2 (3.7)
Metabolic and nutritional	1 (1.8)	0	0
BUN increased	1 (1.8)	0	0
Creatinine increased	1 (1.8)	0	0
Respiratory system	5 (8.8)	5 (8.9)	2 (3.7)
Dyspnea	0	1 (1.8)	0
Eosinophilic pneumonia	1 (1.8)	0	0
Lung disorder	1 (1.8)	0	0
Lung fibrosis	1 (1.8)	0	0
Lung infiltration nos	1 (1.8)	1 (1.8)	0
Pneumonia	1 (1.8)	1 (1.8)	2 (3.7)
Pneumonitis	1 (1.8)	1 (1.8)	0
Respiratory failure	0	1 (1.8)	0
Skin and appendages	1 (1.8)	0	0
Pruritus	1 (1.8)	0	0

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) before the crossover date were considered.
AE = adverse event; BUN = blood urea nitrogen; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; INV = Investigator's; N = number of subjects in each treatment group; n = number of subjects with specified criteria; nos = not otherwise specified; TEMSR = temsirolimus.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.

During the crossover period, 1 subject discontinued treatment due to the AEs of asthenia and pleural effusion (Table 15).

Table 15. Number (%) of Subjects Reporting Adverse Events Leading to Treatment Discontinuation (Crossover Period)

Body System[a] Adverse Event	TEMSR 175/75 mg (N=7) n (%)
Any adverse event	1 (14.3)
Body as a whole	1 (14.3)
Asthenia	1 (14.3)
Respiratory system	1 (14.3)
Pleural effusion	1 (14.3)

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) after the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

Dose Reductions or Temporary Discontinuations due to AEs: The number and percentage of subjects who had dose reductions due to an AE are presented in Table 16.

In the Investigator's choice group, AEs leading to dose reduction in more than 1 subject were thrombocytopenia, leukopenia, and weight loss. In the temsirolimus 175/75 mg group, AEs leading to dose reduction in more than 1 subject were thrombocytopenia, asthenia, mucositis, fever, anemia, and neutropenia. In the temsirolimus 175/25 mg group, AEs leading to dose reduction in more than 1 subject were thrombocytopenia, neutropenia, infection, and diarrhea.

Table 16. Number (%) of Subjects Reporting Adverse Events Leading to Dose Reduction—Safety Population

Body System[a] Adverse Event	TEMSR 175/75 mg (N=57) n (%)	TEMSR 175/25 mg (N=56) n (%)	INV CHOICE (N=54) n (%)
Any adverse event	38 (66.7)	27 (48.2)	7 (13.0)
Body as a whole	8 (14.0)	3 (5.4)	1 (1.9)
Abscess	0	1 (1.8)	0
Asthenia	5 (8.8)	0	1 (1.9)
Fever	2 (3.5)	0	1 (1.9)
Infection	0	2 (3.6)	0
Malaise	0	0	1 (1.9)
Neutropenic fever	1 (1.8)	0	0
Cardiovascular system	1 (1.8)	0	0
Angina pectoris	1 (1.8)	0	0
Digestive system	6 (10.5)	3 (5.4)	0
Anorexia	1 (1.8)	0	0
Diarrhea	0	2 (3.6)	0
Liver function tests abnormal	1 (1.8)	0	0
Mouth ulceration	1 (1.8)	0	0
Mucositis	3 (5.3)	1 (1.8)	0
Rectal hemorrhage	0	1 (1.8)	0
Ulcerative stomatitis	1 (1.8)	0	0
Hemic and lymphatic system	29 (50.9)	21 (37.5)	6 (11.1)
Anemia	2 (3.5)	0	1 (1.9)
Leukopenia	0	0	2 (3.7)
Lymphopenia	0	0	1 (1.9)
Neutropenia	3 (5.3)	5 (8.9)	1 (1.9)
Thrombocytopenia	25 (43.9)	20 (35.7)	4 (7.4)
Metabolic and nutritional	1 (1.8)	1 (1.8)	2 (3.7)
Bilirubinemia	1 (1.8)	0	0
Peripheral edema	0	1 (1.8)	0
SGOT increased	1 (1.8)	0	0
SGPT increased	1 (1.8)	0	0
Weight loss	0	0	2 (3.7)
Respiratory system	2 (3.5)	0	1 (1.9)
Cough increased	0	0	1 (1.9)
Dyspnea	1 (1.8)	0	0
Lung disorder	0	0	1 (1.9)
Pneumonia	1 (1.8)	0	0
Rhinitis	0	0	1 (1.9)
Skin and appendages	2 (3.5)	2 (3.6)	0
Acne	1 (1.8)	0	0
Herpes zoster	0	1 (1.8)	0
Pruritus	1 (1.8)	0	0
Rash	1 (1.8)	1 (1.8)	0
Urogenital system	0	1 (1.8)	0
Kidney function abnormal	0	1 (1.8)	0

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) before the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; INV = Investigator's; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

During the crossover period, 5 subjects had AEs that led to a dose reduction (Table 17).

Table 17. Number (%) of Subjects Reporting Adverse Events Leading to Dose Reduction (Crossover Period)

Body System[a] Adverse Event	TEMSR 175/75 mg (N=7) n (%)
Any adverse event	5 (71.4)
Body as a whole	1 (14.3)
Abdominal pain	1 (14.3)
Back pain	1 (14.3)
Digestive system	1 (14.3)
Nausea	1 (14.3)
Vomiting	1 (14.3)
Hemic and lymphatic system	5 (71.4)
Leukopenia	1 (14.3)
Thrombocytopenia	4 (57.1)

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) after the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

Dose Delays Due to AEs: The number and percentage of subjects who had dose delays due to an AE are presented in Table 18. AEs leading to dose delays were more common in the temsirolimus 175/75 mg and temsirolimus 175/25 mg groups than in the Investigator's choice group (occurring in 84.2%, 76.8%, and 48.1% of subjects, respectively).

Table 18. Number (%) of Subjects Reporting Adverse Events Leading to Dose Delay-Safety Population

Body System[a] Adverse Event	TEMSR 175/75 mg (N=57) n (%)	TEMSR 175/25 mg (N=56) n (%)	INV CHOICE (N=54) n (%)
Any adverse event	48 (84.2)	43 (76.8)	26 (48.1)
Body as a whole	23 (40.4)	12 (21.4)	3 (5.6)
Abdominal pain	1 (1.8)	0	0
Abscess	0	1 (1.8)	0
Accidental injury	0	1 (1.8)	0
Asthenia	9 (15.8)	3 (5.4)	0
Back pain	0	2 (3.6)	0
Cellulitis	1 (1.8)	0	0
Chest pain	1 (1.8)	0	1 (1.9)
Chills	1 (1.8)	0	0
Fever	4 (7.0)	1 (1.8)	2 (3.7)
Flu syndrome	3 (5.3)	1 (1.8)	0
General physical health deterioration	0	2 (3.6)	0
Headache	1 (1.8)	0	0
Infection	6 (10.5)	6 (10.7)	0
Neoplasm	0	1 (1.8)	0
Neutropenic fever	3 (5.3)	0	0
Sepsis	1 (1.8)	0	0
Cardiovascular system	2 (3.5)	3 (5.4)	1 (1.9)
Angina pectoris	1 (1.8)	0	0
Cerebrovascular accident	0	1 (1.8)	0
Deep vein thrombosis	1 (1.8)	1 (1.8)	0
Heart failure	0	0	1 (1.9)
Syncope	1 (1.8)	0	0
Ventricular tachycardia	0	1 (1.8)	0
Digestive system	16 (28.1)	7 (12.5)	1 (1.9)
Anorexia	2 (3.5)	0	0
Constipation	1 (1.8)	0	0
Diarrhea	4 (7.0)	2 (3.6)	0
Enteritis	0	1 (1.8)	0
Gamma glutamyl transpeptidase increased	1 (1.8)	0	0
Gastritis	1 (1.8)	0	0
Gastroenteritis	1 (1.8)	0	0
Gastrointestinal hemorrhage	1 (1.8)	0	0
Liver damage	1 (1.8)	0	0
Melena	0	0	1 (1.9)
Mouth pain	1 (1.8)	0	0
Mouth ulceration	1 (1.8)	0	0
Mucositis	4 (7.0)	1 (1.8)	0
Nausea	0	1 (1.8)	0
Periodontitis	1 (1.8)	0	0
Rectal disorder	0	1 (1.8)	0
Rectal hemorrhage	1 (1.8)	0	0
Stomatitis	0	2 (3.6)	0
Tooth disorder	0	1 (1.8)	0
Ulcerative stomatitis	1 (1.8)	0	0
Hemic and lymphatic system	35 (61.4)	31 (55.4)	21 (38.9)
Anemia	5 (8.8)	0	3 (5.6)
Hemolytic anemia	0	0	1 (1.9)
Leukopenia	2 (3.5)	1 (1.8)	8 (14.8)
Lymphoma	0	2 (3.6)	0
Neutropenia	7 (12.3)	8 (14.3)	8 (14.8)
Thrombocytopenia	33 (57.9)	30 (53.6)	13 (24.1)
Metabolic and nutritional	6 (10.5)	4 (7.1)	1 (1.9)
Creatinine increased	3 (5.3)	1 (1.8)	0

Table 18. Number (%) of Subjects Reporting Adverse Events Leading to Dose Delay-Safety Population

Body System[a] Adverse Event	TEMSR 175/75 mg (N=57) n (%)	TEMSR 175/25 mg (N=56) n (%)	INV CHOICE (N=54) n (%)
Dehydration	1 (1.8)	1 (1.8)	0
Hypokalemia	1 (1.8)	1 (1.8)	0
Peripheral edema	0	1 (1.8)	0
SGOT increased	0	0	1 (1.9)
SGPT increased	0	0	1 (1.9)
Weight loss	1 (1.8)	0	0
Musculoskeletal system	0	1 (1.8)	0
Arthralgia	0	1 (1.8)	0
Nervous system	1 (1.8)	1 (1.8)	0
Neuropathy	1 (1.8)	0	0
Somnolence	0	1 (1.8)	0
Thinking abnormal	1 (1.8)	0	0
Respiratory system	12 (21.1)	10 (17.9)	4 (7.4)
Bronchitis	1 (1.8)	2 (3.6)	1 (1.9)
Cough increased	2 (3.5)	1 (1.8)	1 (1.9)
Dyspnea	1 (1.8)	1 (1.8)	1 (1.9)
Epistaxis	0	1 (1.8)	0
Lung disorder	1 (1.8)	1 (1.8)	0
Lung infiltration nos	0	1 (1.8)	1 (1.9)
Pneumonia	7 (12.3)	4 (7.1)	2 (3.7)
Pneumonitis	1 (1.8)	0	0
Sinusitis	0	1 (1.8)	0
Upper respiratory infection	2 (3.5)	0	0
Skin and appendages	9 (15.8)	4 (7.1)	0
Acne	1 (1.8)	0	0
Dry skin	0	1 (1.8)	0
Fungal dermatitis	1 (1.8)	0	0
Herpes simplex	1 (1.8)	0	0
Herpes zoster	1 (1.8)	1 (1.8)	0
Pruritic rash	1 (1.8)	0	0
Pruritus	3 (5.3)	0	0
Rash	3 (5.3)	1 (1.8)	0
Urticaria	0	1 (1.8)	0
Special senses	2 (3.5)	2 (3.6)	0
Conjunctivitis	0	1 (1.8)	0
Corneal ulcer	0	1 (1.8)	0
Eye disorder	1 (1.8)	0	0
Taste loss	1 (1.8)	0	0
Urogenital system	1 (1.8)	2 (3.6)	0
Dysuria	0	1 (1.8)	0
Kidney failure	1 (1.8)	0	0
Kidney function abnormal	0	1 (1.8)	0

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) before the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; INV = Investigator's; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.

a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

The number and percentage of subjects who had dose delays due to an AE (crossover period) are presented in Table 19.

Table 19. Number (%) of Subjects Reporting Adverse Events Leading to Dose Delay (Crossover Period)

Body System[a] Adverse Event	TEMSR 175/75 mg (N=7) n (%)
Any adverse event	6 (85.7)
Body as a whole	2 (28.6)
Asthenia	1 (14.3)
Cellulitis	1 (14.3)
Infection	1 (14.3)
Hemic and lymphatic system	6 (85.7)
Anemia	2 (28.6)
Leukopenia	1 (14.3)
Neutropenia	1 (14.3)
Thrombocytopenia	5 (71.4)
Respiratory system	3 (42.9)
Dyspnea	1 (14.3)
Pleural disorder	1 (14.3)
Pneumonia	1 (14.3)
Upper respiratory infection	1 (14.3)

AEs were coded with COSTART 5th Edition with Sponsor internal modification.
All AEs that occurred (started) after the crossover date were considered.
AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Body system totals for the number of subjects are not necessarily the sum of the individual AEs since a subject may report 2 or more different AEs in the same body system.

Deaths: A summary of deaths that occurred during this study is presented in Table 20.

As expected due to the nature of the disease under study, a majority of subjects in each treatment arm died during the study and during the follow-up period. In a large majority of cases, in all treatment groups, the cause of death was disease progression.

Table 20. Summary of Deaths-ITT Population

Parameter	TEMSR 175/75 mg (N=57) n (%)	TEMSR 175/25 mg (N=56) n (%)	INV CHOICE (N=56) n (%)
All deaths	40 (70.2)	41 (73.2)	37 (66.1)
Deaths within 14 days of last dose	4 (7.0)	2 (3.6)	1 (1.8)
Deaths after 14 days from last dose	36 (63.2)	39 (69.6)	36 (64.3)
Reason for death[a]			
Adverse event	2 (5.0)	3 (7.3)	0
Disease progression	36 (90.0)	35 (85.4)	35 (94.6)
Other	2 (5.0)	3 (7.3)	1 (2.7)
Reason not specified	0	0	1 (2.7)

INV = Investigator's; N = number of subjects in each treatment group; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Percentages are based on number of subjects who died in each treatment group.

During the crossover period, 4 subjects died, all after 14 days from last dose (Table 21). The cause of death was disease progression in 3 of these 4 subjects.

Table 21. Summary of Deaths—ITT Population (Crossover Period)

Parameter	TEMSR 175/75 mg (N=7) n (%)
All deaths	4 (57.1)
Deaths after 14 days from last dose	4 (57.1)
Reason for death[a]	
Disease progression	3 (75.0)
Other	1 (25.0)

N = number of subjects; n = number of subjects with specified criteria; TEMSR = temsirolimus.
a. Percentages are based on number of subjects who died in each treatment group.

CONCLUSIONS: Temsirolimus administered IV in 3 weekly doses of 175 mg followed by weekly doses of 75 mg led to statistically significant benefits over Investigator's choice treatment in subjects with relapsed/refractory MCL with respect to PFS (median 4.8 months versus 1.9 months), ORR (22.2% versus 1.9%), TTP (median 5.2 months versus 1.9 months), and TTF (median 3.1 months versus 1.7 months). Although temsirolimus was associated with higher incidences of Grade 3 or 4 TEAEs than Investigator's choice treatment (88.9% versus 67.9%), these events did not generally lead to discontinuation of treatment with temsirolimus. In fact, subjects were on treatment in the temsirolimus 175/75 mg group longer than subjects in the Investigator's choice group (median 12.1 weeks versus 4.6 weeks) because they were not experiencing disease progression or AEs severe enough to lead to discontinuation. AEs leading to dose reduction or delay were more frequent in the temsirolimus 175/75 mg group than in the Investigator's choice group; however, it should be noted that many of these reductions were adjustments to the initial 175 mg doses and that the longer subjects were on treatment the greater the likelihood of dose delays. The most frequent TEAEs for temsirolimus 175/75 mg affected the body as a whole, the hemic and lymphatic, digestive, and respiratory systems, and the skin and appendages. Overall, the safety profile of temsirolimus in this study was consistent with the known safety profile based on other studies in the temsirolimus clinical development program and the expected safety profile for subjects with hematologic cancers.

Overall, single-agent temsirolimus (175 mg IV weekly followed by 75 mg IV weekly) offers a promising treatment option that prolongs PFS and has an acceptable safety profile for subjects with relapsed/refractory MCL.