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

PROTOCOL NO.: 3066K1-2217-AP (B1771002)

PROTOCOL TITLE: A Phase 2, Non-Randomized, Open-Label Study of Temsirolimus (CCI-779) in Subjects With Advanced Renal Cell Carcinoma

Study Center(s): Twenty-six (26) centers took part in the study and enrolled subjects: 6 in China; 4 in the Republic of Korea and 16 in Japan.

Study Initiation Date and Final Completion Dates: 05 June 2007 to 15 March 2012

Phase of Development: Phase 2

Study Objectives:

Safety: To assess the rate of adverse events (AEs) in a Japanese, Chinese, and Korean renal cell carcinoma (RCC) population treated with temsirolimus.

Efficacy: Determine the clinical benefit rate (the percentage of subjects who achieve complete response [CR], partial response [PR], or stable disease [SD] ≥24 weeks).

The additional efficacy objectives of the study included estimation of progression-free survival (PFS), objective response rate (ORR) (the percentage of subjects who achieved CR or PR), duration of objective response, time to treatment failure (TTF), and overall survival (OS).

METHODS

Study Design:

This was a phase 2, nonrandomized, open-label, multicenter, outpatient study of temsirolimus in approximately 80 subjects with advanced RCC.

A subset (n = 6) of the Japanese subjects received 20 mg/m^2 of temsirolimus. This subset was referred to as Group A. Subjects in Group A were hospitalized for the first 4 doses and had frequent physical and laboratory evaluations. The safety information obtained served as the basis to evaluate the tolerability of 20 mg/m^2 of temsirolimus in this population.

All other subjects in this study were part of Group B. These subjects received a flat dose of 25 mg of temsirolimus.

Subjects received temsirolimus until disease progression, unacceptable toxicities, or withdrawal of consent. Tumor progression was assessed locally and by independent read, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST). Safety parameters were evaluated throughout the study.

The Screening period was up to 4 weeks in duration and post-therapy follow-up visits were conducted approximately every 8 weeks after the subject discontinued use of the test article until the subject's death. Subjects were followed for survival. The study ended for all other subjects when the last subject died or up to 4 years from the first dose for the last subject enrolled, whichever came first.

The schedule of activities for subjects in Group A and Group B are summarized in Table 1 and Table 2, respectively. Tumor assessment flow chart has been summarized in Table 3.

Table 1. Schedule of Activities for Group A Subjects (20 mg/m^2 Dose)

Visit Activity	**Screening[a]**		**Treatment Phase[b]**														
Week of study	**-4 to 1**	**-2 to 1**	**1**				**2**		**3**		**4**				**5**	**6+**	**WD[c]**
Study day	**-28 to 1**	**-14 to 1**	**1**	**2**	**4**	**5**	**8**	**11**	**15**	**18**	**22**	**23**	**25**	**26**	**29**	**36**	
Cycle day			**1**	**2**	**4**	**5**	**1**	**4**	**1**	**4**	**1**	**2**	**4**	**5**	**1**	**1**	
Study visit window								±1		±1					±2	±2	
Informed consent	X																
Demographic data	X																
Medical, cardiac, pulmonary and disease history	X																
Hospitalization			X														
Physical examination		X	X[d]				X[d]		X[d]		X[d]				X[d]	X[d]	X
Inclusion and exclusion criteria	X	X															
Prior and current medications	X	Continually															
ECOG performance status		X	X[d]				X[d]		X[d]		X[d]				X[d]	X[d]	X
Vital signs		X	X[d]	X	X	X	X[d]		X[d]		X[d]	X	X	X	X[d]	X[d]	X
Radiographic evaluations	See tumor assessment flow chart (Table 3)																
ECG[e]	X		X								X				X	X	X
ECHO or MUGA	X																X
Pulmonary function test	X																X
Pulse oximetry		X	X				X		X		X				X	X	X
CBC with differential		X	X[f]		X		X[f]	X	X[f]	X	X[f]		X		X[f]	X[f]	X
$HgbA_{1C}$		X[g]														X[g]	X[g]
Fasting chemistry/lipid panel		X	X[f,h]				X[f,h]		X[f,h]		X[f,h]				X[f,h]	X[f,h]	X[h]
Coagulation tests[i]		X									X[f]				X[f]	X[f]	X
Pregnancy tests[j]		X															X
Temsirolimus administration			X				X		X		X				X	X	
CPE number (for sponsor use only)	1	1	2/3	3			4		5		6				7	8	500
Monitor AEs	Continually																
Post-therapy follow-up	X[k]																

Table 1. Schedule of Activities for Group A Subjects (20 mg/m^2 Dose)

Visit Activity	Screening[a]		Treatment Phase[b]														
Week of study	-4 to 1	-2 to 1	1				2		3		4				5	6+	WD[c]
Study day	-28 to 1	-14 to 1	1	2	4	5	8	11	15	18	22	23	25	26	29	36	
Cycle day			1	2	4	5	1	4	1	4	1	2	4	5	1	1	

For subjects who discontinued the active treatment phase for reasons other than PD: 1) tumor assessments performed every 8 weeks from the date of the last tumor assessment until documented PD or until beginning a new cancer treatment; 2) survival information collected approximately every 8 weeks from last day of test article administration (e.g., end of active treatment phase); 3) SAEs that were considered related to test article; 4) new cancer treatment with available current response.
For subjects who discontinued the active treatment phase for PD: 1) survival information collected approximately every 8 weeks from last day of test article administration (e.g., end of active treatment phase); 2) new cancer therapy with available current response; 3) SAEs related to test article.
Abbreviations: AEs = adverse events; CBC = complete blood count; D = Day; ECOG = eastern cooperative oncology group; ECG = electrocardiogram; ECHO = echocardiogram; HgbA1C = glycosylated hemoglobin; MUGA = multiple gated acquisition scan; PD = progressive disease; SAE = serious adverse events; WD = withdrawal visit.

a. The Screening evaluation were completed within 28 days before the first dose of temsirolimus. AE data collection began when the informed consent form was signed.
b. The "treatment phase" was defined as the period of time from the start of treatment until there was evidence of disease progression, or the patient was withdrawn from treatment, and included the 30 days after the last dose of temsirolimus.
c. Withdrawal visit studies were conducted as soon as possible (expected to be performed within 2 weeks) after the decision to withdraw a subject, or after the documentation of PD. Assessment and data collection of concomitant medications and AEs were continued 30 days after last dose of test article.
d. Physical examination including weight (and height, at Screening), ECOG score, and vital signs were done prior to the dose of test article.
e. ECGs were performed pretreatment on Day 1, within 1 hour after stop of 1st temsirolimus infusion, and at end of treatment, and was clinically indicated during the study. If QTc prolongation was evident at the end of treatment, then repeated at least 2 weeks after last dose of test article. All ECGs were submitted for a central independent review. Laboratory assessment to test magnesium, calcium, and potassium on the same day as each ECG timepoint was required. Group A subjects had additional ECGs at Week 4, Week 5, Week 6, and every 4 weeks thereafter.
f. Tests were done within 72 hours and results were available before temsirolimus administration.
g. Glycosylated hemoglobin (HgbA1c) was performed at Screening, approximately every 12 weeks, and at end of treatment.
h. For chemistry/lipid panel, a fasting assessment was recommended. Any abnormal non-fasting values that were not abnormal at Screening required a repeat assessment. Laboratory assessment to test magnesium, calcium, and potassium on the same day as each ECG timepoint was required.
i. Coagulation tests were done at Screening, withdrawal visit, Weeks 4, 5, 6, and every 4 weeks thereafter during treatment phase in Group A. Subjects which received anticoagulants were monitored in Week 1, 2, 3, additionally.
j. For women of childbearing potential, pregnancy test (serum or urine) were done at Screening (within 7 days before Day 1), and at the withdrawal visit.
k. Post-therapy follow-up visits were conducted approximately every 8 weeks after the subject discontinued use of the test article until the subject's death. These visits were conducted by telephone interview (if applicable, as indicated below) and included the following evaluations:
    - Date of death and cause of death, if applicable (by telephone).
    - Tumor assessments--Applicable only if the subject withdrew from the study for reasons other than progression. Radiographic evaluations were continued to be performed every 8 weeks by the Investigator after the last tumor assessments during the post-therapy follow-up period until disease progression was observed or new anticancer treatment (biologic or chemotherapeutic) was initiated or death.
    - Anticancer therapies received after the treatment period (by telephone).
    - AEs were collected for the first 30 days after test article discontinuation. After the 30-day reporting period, only SAEs believed to be related to test article were to be reported.

Table 2. Schedule of Activities for Group B Subjects (25 mg Flat Dose)

			Treatment Phase[a]				
Visit Activity	**Screening[b]**		**Each 4 Weeks of Therapy**				**Withdrawal Visit[c]**
Week of study	**-4 to 1**	**-2 to 1**	**1, 5, 9, 13, 17, 21, 25 etc.)**				
Day (approximate, ±2 days)	**-28 to 1**	**-14 to 1**	**D1**	**D8**	**D15**	**D22**	
Informed consent	X						
Demographic data	X						
Medical and disease history	X						
Cardiac and pulmonary history	X						
Clinic visit		X	X	X	X	X	X
Physical examination[d]		X	X	X	X	X	X
Inclusion and exclusion criteria	X	X					
Prior and current medications	X	Continually					
ECOG performance status[d]		X	X	X	X	X	X
Vital signs[d]		X	X	X	X	X	X
Radiographic evaluations	See tumor assessment flow chart (Table 3)						
ECG	X		X[e]				X
ECHO or MUGA	X						X
Pulmonary function test	X						X
Pulse oximetry		X	X	X	X	X	X
CBC with differential		X	X[f,g]	X[f,g]	X[f,g]	X[f,g]	X
$HgbA_{1C}$		X[h]	X[h]				X[h]
Fasting chemistry/lipid panel		X[i]	X[i,j,f]		X[i,j,f]		X[i]
Coagulation tests[k]		X					X
Pregnancy tests		X[l]					X[l]
Temsirolimus administration			X	X	X	X	
CPE number (for sponsor use only)	1	1	2/3	4	5	6	500
Monitor AEs	Continually						
Post-therapy follow-up	X[m]						

Table 2. Schedule of Activities for Group B Subjects (25 mg Flat Dose)

			Treatment Phase[a]				
Visit Activity	**Screening[b]**		**Each 4 Weeks of Therapy**				**Withdrawal Visit[c]**
Week of study	**-4 to 1**	**-2 to 1**	**1, 5, 9, 13, 17, 21, 25 etc.)**				
Day (approximate, ±2 days)	**-28 to 1**	**-14 to 1**	**D1**	**D8**	**D15**	**D22**	

For subjects who discontinued the active treatment phase for reasons other than PD: 1) tumor assessments performed every 8 weeks from the date of the last tumor assessment until documented PD or until beginning a new cancer treatment; 2) survival information collected approximately every 8 weeks from last day of test article administration (e.g., end of active treatment phase); 3) SAEs that were considered related to test article; 4) new cancer treatment with available current response.

For subjects who discontinued the active treatment phase for PD: 1) survival information collected approximately every 8 weeks from last day of test article administration (e.g., end of active treatment phase); 2) new cancer therapy with available current response; 3) SAEs related to test article.

Abbreviations: AEs = adverse events; CBC = complete blood count; D = Day; ECOG = eastern cooperative oncology group; ECG = electrocardiogram; ECHO = echocardiogram; HgbA1C = glycosylated hemoglobin; MUGA = multiple gated acquisition scan; PD = progressive disease; SAE = serious adverse events; WD = withdrawal visit.

a. The "treatment phase" was defined as the period of time from the start of treatment until there was evidence of disease progression, or the subject was withdrawn from treatment, and included the 30 days after the last dose of temsirolimus.
b. The Screening evaluation was completed within 28 days before the first dose of temsirolimus. AE data collection began when the informed consent form was signed.
c. Withdrawal visit studies were conducted as soon as possible after the decision to withdraw a subject, or after the documentation of PD. Assessment and data collection of concomitant medications and AEs continued until 30 days after last dose of test article.
d. Physical examination including weight (and height at Screening), ECOG score, and vital signs were done prior to test article administration.
e. ECGs were performed pretreatment on Day 1, within 1 hour after stop of 1st temsirolimus infusion, and at end of treatment, and as clinically indicated during the study. If QTc prolongation was evident at end of treatment, then repeated at least 2 weeks after last dose of test article. All ECGs were to be submitted for a central independent review. Laboratory assessment to test magnesium, calcium, and potassium on the same day as each ECG timepoint was required.
f. Tests were done within 72 hours and results were available before temsirolimus administration.
g. For subjects remaining in the study for longer than 16 weeks, CBC was performed every 2 weeks, if clinically appropriate.
h. Glycosylated hemoglobin (HgbA1c) was performed at Screening, approximately every 12 weeks, and at end of treatment.
i. For chemistry/lipid panel, a fasting assessment was recommended. Any abnormal non-fasting values that were not abnormal at Screening required a repeat assessment. Laboratory assessment to test magnesium, calcium, and potassium on the same day as each ECG timepoint was required.
j. For subjects remaining in the study for longer than 16 weeks, chemistry/lipid panel was performed every 4 weeks, if clinically appropriate.
k. Coagulation tests were done at Screening and Withdrawal visits. Subjects receiving anticoagulants were monitored weekly for the first 4 weeks of treatment, then every 4 weeks.
l. For women of childbearing potential, pregnancy testing (serum or urine) was, done at Screening (within 7 days before enrollment) and at the withdrawal visit.
m. Post-therapy follow-up visits were conducted approximately every 8 weeks after the subject discontinued use of the test article until the subject's death. These visits were conducted by telephone interview (if applicable, as indicated below) and included the following evaluations:
    - Date of death and cause of death, if applicable (by telephone).
    - Tumor assessments--Applicable only if the subject withdrew from the study for reasons other than progression. Radiographic evaluations were continued to be performed every 8 weeks by the Investigator after the last tumor assessments during the post-therapy follow-up period until disease progression was observed or new anticancer treatment (biologic or chemotherapeutic) was initiated or death.
    - Anticancer therapies received after the treatment period (by telephone).
    - AEs were collected for the first 30 days after test article discontinuation. After the 30-day reporting period, only SAEs believed to be related to test article were to be reported.

Table 3. Tumor Assessment Flow Chart

Type of Tumor Assessment	Screening[a] (Within 4 Weeks Before Day 1)	Treatment Period Every 8 Weeks (±5 days) After Day 1[b]	Confirmation CR or PR[c] (Not Less Than 4 Weeks From The Previous Assessment)	Withdrawal Visit[d] (Within 4 Weeks After The Last Dose of Temsirolimus) and Long Term Follow-up (If Documented PD Did Not Occur During Study Treatment)
Brain CT/MRI	Required			
Chest CT	Required	Required	Required	Required
Abdominal/Pelvic CT	Required	Required	Required	Required
Radionuclide bone scan	Required		Required	

Notes: Contrast was used unless contraindicated in the subject.
Treatment period was defined as the time from the first dose of temsirolimus until there was evidence of disease progression or withdrawal from the study (provided the treatment was tolerated).
Long-term follow-up period: Radiographic evaluations were continued to be done every 8 weeks by the Investigator during the post-therapy follow-up period until disease progression was observed or new anticancer treatment (biologic or chemotherapeutic) was initiated or death.
Examinations were to be performed at any time if there was clinical suspicion of disease progression, at the discretion of the Investigator. The lesion measurements were expected to be completely documented within 2 weeks after the last assessment date for a specific time point. If PD was confirmed per RECIST subjects were expected to discontinue therapy and begin the follow-up phase of the trial.
Abbreviations: CT = computed tomography; CR = complete response; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; US = ultrasound.

a. Scans for initial tumor assessment were done within 4 weeks before enrollment. During the treatment period, scans for tumor assessments were done approximately every 8 weeks starting from enrollment (± 5 Days). The radiologic assessments were not adjusted depending on treatment hold. Assessments were expected on Day 57, Day 113, Day 169, etc, for all subjects. Assessment of clinical lesions (both measurable and nonmeasurable) were performed in the same timeframe as radiologic examinations. Previously obtained assessments were acceptable to be used as Screening evaluations if the radiographic film (or digital data) was obtained within 4 weeks before enrollment and obtained by spiral CT (5-mm slice thickness contiguous) or conventional CT (10-mm slice thickness contiguous). MRI was also an accepted imaging method. The previously obtained assessments were performed as described below so that same technique was used throughout the study.
    1. CT and MRI were the best available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI were performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT was performed using a 5 mm contiguous reconstruction algorithm. This applied to tumors of the chest, abdomen and pelvis. Maximum slice thickness defined was 10 mm (5 mm or 7 mm recommended).
    2. All measurements were taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations were performed as closely as possible to enrollment and never more than 4 weeks before enrollment.
    3. The same method of assessment and the same technique was used to characterize each identified and reported lesion at Baseline and during follow-up.
    4. Clinical lesions were only considered measurable when they were superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, was recommended.
    5. In general, US was not used to measure tumor lesions. It was, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US was also useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
    6. Cytology and histology could be used to differentiate between PR and complete response CR in rare cases.
b. Scans were continued to be done on all subjects who received test article, including subjects who discontinued use of the test article for any reason other than disease progression, until disease progression was noted.
c. Required series of scans, at the 4-week timepoint, if previous tumor assessment time point documented a response (ie, CR or PR).
d. Scans were performed at the withdrawal visit if not done within 4 weeks before discontinuation for subjects who had not already demonstrated objective disease progression.

Number of Subjects (Planned and Analyzed): A total of 82 subjects were enrolled and received temsirolimus: 6 in Group A (20 mg/m^2) in Japan and 76 in Group B (25 mg/body, ie, a flat dose of 25 mg). Of the 76 subjects in Group B, 14 were in Japan, 30 in Korea, and 32 in China. All 82 enrolled subjects were included in both the intent-to-treat (ITT) and safety populations. The evaluable population consisted of 79 subjects in total.

Diagnosis and Main Criteria for Inclusion: Subjects with histologically confirmed, advanced (Stage IV or recurrent disease) RCC according to the American Joint Committee on Cancer (AJCC) staging and classification criteria, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, had at least 1 measurable lesion per RECIST, and aged ≥20 years and <75 years for Group A and ≥20 years for Group B, and had to be of Japanese, Chinese, or Korean ethnicity. Subjects were ineligible to participate in this study if any of the following criteria were met: use of prior targeted, chemotherapeutic, cytokine-based, or other investigational agents for the treatment of RCC within 4 weeks before the first dose of test article; evidence of current or prior central nervous system (CNS) metastases, in the past 5 years had other prior malignancy (except basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ).

Study Treatment: Temsirolimus was administered only to subjects who were eligible and had provided signed informed consent. Once temsirolimus was assigned to a subject, it was not to be reassigned to another subject. In Japan, a group of 6 subjects received a dose of 20 mg/m^2 of temsirolimus administered intravenously (IV) once weekly (Group A). All remaining subjects (a total of 76 subjects in Japan, China, and Korea) received a flat dose of 25 mg of temsirolimus administered IV once weekly (Group B). Dose adjustments according to protocol-specified guidelines were allowed.

Efficacy Endpoints:

Primary Efficacy Endpoint: The primary efficacy endpoint of this study was clinical benefit rate (the percentage of subjects who achieved CR, PR, or SD ≥24 weeks) by RECIST.

Secondary Efficacy Endpoint: The secondary efficacy endpoints were those listed below:

- PFS, which was the interval from the date of enrollment until the earlier date of progression or death, censored at the last tumor evaluation date.
- ORR (CR + PR).
- Duration of objective response, which was measured from the time at which measurement criteria were met for CR or PR (whichever status was recorded first) until the first date on which recurrence or progressive disease (PD) was objectively documented, taking as the reference for PD the smallest sum of the longest diameters (LDs) recorded since enrollment.
- TTF, which was the interval from the date of enrollment until the earlier date of progression or death (any cause), withdrawal from treatment owing to AE, subject

refusal, loss to follow-up (censored at the last contact date), or further anticancer therapy before documented progression (whichever occurred first).

- OS, which was recorded from the date of enrollment until the date of death, censored at the last date on which the subject was known to be alive.

Pharmacokinetic Evaluation: Temsirolimus and sirolimus, a major metabolite, were measured in whole blood samples from 6 Japanese subjects at the following timepoints (Group A): 0 (pre-dose), 0.5 (end of infusion), 1, 2, 6, 24, 72, and 96 hours during weeks 1 and 4 of treatment, and at 0 hour on study weeks 2, 3, and 5. In all remaining study subjects (Group B), whole blood samples were collected at 0 hour during Weeks 1 through 5, and during Week 4 at 2 and 72 hours.

Safety Evaluations: Safety evaluations were conducted at protocol-specified time points and included physical examination, laboratory assessments, monitoring of AEs, and serious adverse event (SAE) evaluations throughout the study. Other safety assessments included electrocardiogram (ECG), echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans, pulmonary function tests (PFT), oxygen saturation (O_2 sat) by pulse oximetry, computed tomography (CT) scans, and monitoring of concomitant medications for the management of AEs.

For efficacy evaluations, tumor assessments were scheduled every 8 weeks until disease progression using CT scans of the chest, abdomen, and pelvis.

A detailed description of these evaluations has been summarized in Table 1 and Table 2.

AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 3.0. Medical Dictionary for Regulatory Activities (MedDRA) dictionary terminology (version 15.0) was used to categorize the reported AEs.

An independent Data Safety Monitoring Board (DSMB) reviewed the safety data, including SAEs, from the Group A subjects to confirm the dose limiting toxicities. All subjects (Group A and Group B) who received at least 1 dose of test article were included in the review of safety by the DSMB.

Statistical Methods:

Safety and efficacy analyses were descriptive in nature. The various variables collected during this study were summarized using descriptive statistics. For continuous variables, the descriptive statistics included n, mean, median, standard deviation, and range (minimum, maximum). For categorical variables, the descriptive statistics include the count in each category, the total n, and percentage. Analyses were basically performed by treatment group and overall, but this study did not intend to compare the outcomes between treatment groups. Key summary tables were also generated by region regarding Group B only.

The primary efficacy analysis was based on the intent-to-treat (ITT) population, defined as all subjects enrolled in the study. Additional analyses for efficacy endpoints were also done using the evaluable population, defined as all subjects who had no protocol violation that could confound the interpretation of study results, received at least 1 dose of temsirolimus, and underwent at least 1 follow-up tumor assessment approximately 8 weeks after starting treatment unless the subject discontinued administration of temsirolimus because of disease progression or death. Safety data were analyzed on the basis of available data in the safety population.

RESULTS

Subject Disposition and Demography: A total of 82 subjects were enrolled and received temsirolimus: 6 in Group A (20 mg/m^2) in Japan and 76 in Group B (25 mg/body, ie, a flat dose of 25 mg) (Table 4). Of the 76 subjects in Group B, 14 were in Japan, 30 in Korea, and 32 in China. All 82 enrolled subjects were included in both the ITT and safety populations. The evaluable population consisted of 79 subjects in total.

Table 4. Summary of the Subject Population, All Subjects

	Treatment		
	Group A (20 mg/m^2) (N=6)	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Population (n)			
Screen failures[a]	NA	NA	22
Enrolled subjects	6	76	82
Received test article	6	76	82
Analysis populations			
Intent-to-treat population	6	76	82
Evaluable population	6	73	79
Safety population	6	76	82

Abbreviation: NA = not applicable; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria.

a. This row displays only the total number of subjects because this procedure was performed prior to allocation of subjects to dose group.

A total of 59 subjects (72.0%) died and 23 subjects (28.0%) were lost to follow-up; 5 subjects and 54 subjects died, and 1 subject and 22 subjects lost in follow-up in Group A and Group B, respectively.

All 82 subjects discontinued the treatment (Table 5). Common primary reasons for the treatment discontinuation were disease progression (45 subjects [54.9%]) and AEs (22 subjects [26.8%]).

Table 5. Reasons for Conclusion of the Treatment Phase, ITT Population

	Treatment		
Conclusion Status Reason[a]	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Discontinued (n, %)	6 (100)	76 (100)	82 (100)
Adverse event	4 (66.7)	18 (23.7)	22 (26.8)
Death	0	5 (6.6)	5 (6.1)
Disease progression	2 (33.3)	43 (56.6)	45 (54.9)
Other	0	4 (5.3)	4 (4.9)
Subject request	0	5 (6.6)	5 (6.1)
Symptomatic deterioration	0	1 (1.3)	1 (1.2)

Abbreviation: ITT = intent-to-treat; N = Total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

Demographic and Other Baseline Characteristics:

Table 6 shows the demographic and baseline characteristics for the ITT population. Of the 82 subjects enrolled in the study, 59 subjects (72.0%) were men and 23 subjects (28.0%) were women. The age range was 26 to 83 years old, with a median age of 55.0 years old. All subjects had a Baseline ECOG PS of 0 (32 subjects, 39.0%) or 1 (50 subjects, 61.0%). A total of 56 subjects (68.3%) were in the intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk group, 19 subjects (23.2%) were in the favorable risk group, and 6 subjects (7.3%) were in the poor risk group, and 1 was unknown.

Table 6. Demographic and Other Baseline Characteristics, ITT Population

	Treatment		
Characteristic	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Age (Years)			
N	6	76	82
Mean	59.67	55.2	55.52
Standard Deviation	10.29	11.52	11.43
Minimum	49	26	26
Maximum	74	83	83
Median	57.5	55	55
Age category (n, %)			
<65	4 (66.7)	58 (76.3)	62 (75.6)
≥65	2 (33.3)	18 (23.7)	20 (24.4)
Sex (n, %)			
Female	0	23 (30.3)	23 (28.0)
Male	6 (100)	53 (69.7)	59 (72.0)
Race (n, %)			
Chinese	0	32 (42.1)	32 (39.0)
Japanese	6 (100)	14 (18.4)	20 (24.4)
Korean	0	30 (39.5)	30 (36.6)

Table 6. Demographic and Other Baseline Characteristics, ITT Population

	Treatment		
Characteristic	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Weight (Kg)			
N	6	76	82
Mean	69.72	65.25	65.58
Standard Deviation	12.83	10.67	10.81
Minimum	50.7	45.5	45.5
Maximum	88.6	96	96
Median	69.5	65	66.5
Height (cm)			
N	6	76	82
Mean	170.57	165.33	165.71
Standard Deviation	6	8.23	8.17
Minimum	162.8	148	148
Maximum	179.6	185	185
Median	169.25	165.5	166.95
Baseline ECOG Performance Status (n, %)			
0	5 (83.3)	27 (35.5)	32 (39.0)
1	1 (16.7)	49 (64.5)	50 (61.0)
Abnormal medical history (n, %)			
No	0	14 (18.4)	14 (17.1)
Yes	6 (100)	62 (81.6)	68 (82.9)
Complication (n, %)			
No	0	22 (28.9)	22 (26.8)
Yes	6 (100)	54 (71.1)	60 (73.2)
MSKCC risk group (n, %)			
Favorable	0	19 (25.0)	19 (23.2)
Intermediate	4 (66.7)	52 (68.4)	56 (68.3)
Poor	2 (33.3)	4 (5.3)	6 (7.3)
Unknown	0	1 (1.3)	1 (1.2)
Modified risk group (out of 6 factors)			
<3 factors	3 (50.0)	46 (60.5)	49 (59.8)
≥3 factors	3 (50.0)	29 (38.2)	32 (39.0)
Unknown	0	1 (1.3)	1 (1.2)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; MSKCC = Memorial Sloan-Kettering Cancer Center; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria.

Efficacy Results:

The tumor assessment-related endpoints (clinical benefit rate, ORR, duration of objective response, and PFS) were analyzed based on both Investigator's and independent tumor assessments.

Primary Endpoint Results:

Table 7 shows the best overall response for the ITT population. Although there were no CRs, 11.0% of subjects had PRs and 65.9% had SD for at least 8 weeks according to the Investigator's assessment, 3.7% of subjects had PRs and 70.7% had SD for at least 8 weeks according to the independent assessment.

Table 7. Best Overall Response, ITT Population

	Treatment		
Best Overall Response (n, %)	**Group A (20 mg/m^2) (N = 6)**	**Group B (25 mg/body) (N = 76)**	**Total (N = 82)**
Investigator's assessment			
Partial response	0	9 (11.8)	9 (11.0)
Stable disease[a]	5 (83.3)	49 (64.5)	54 (65.9)
Stable disease ≥24 weeks[b]	3 (50.0)	28 (36.8)	31 (37.8)
Progressive disease	1 (16.7)	13 (17.1)	14 (17.1)
Indeterminate[c]	0	1 (1.3)	1 (1.2)
No. of post-baseline tumor assessment	0	4 (5.3)	4 (4.9)
Independent assessment			
Partial response	0	3 (3.9)	3 (3.7)
Stable disease[a]	4 (66.7)	54 (71.1)	58 (70.7)
Stable disease ≥24 weeks[b]	2 (33.3)	27 (35.5)	29 (35.4)
Progressive disease	2 (33.3)	14 (18.4)	16 (19.5)
Indeterminate[c]	0	1 (1.3)	1 (1.2)
No. of post-baseline tumor assessment	0	4 (5.3)	4 (4.9)

Abbreviation: ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number.

a. Must have met the stable disease criteria at least once after enrollment at a minimum of 8 weeks.
b. Must have met the stable disease criteria at least once after enrollment at a minimum of 24 weeks.
c. Had assessment of stable disease or unconfirmed response prior to 8 weeks after enrollment.

The primary efficacy endpoint of this study was the clinical benefit rate as assessed by RECIST. The clinical benefit rate was the percentage of subjects who had CR, PR, or SD for at least 24 weeks. Table 8 shows the clinical benefit rate for the ITT population. The clinical benefit was observed in 40 of 82 subjects and the clinical benefit rate was 48.8% (95% confidence interval [CI]: 37.6% to 60.1%) according to the Investigator's assessment. The clinical benefit according to the independent assessment was observed in 32 of 82 subjects and the clinical benefit rate was 39.0% (95% CI: 28.4% to 50.4%).

Table 8. Clinical Benefit Rate, ITT Population

	Treatment		
Clinical Benefit Rate	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Investigator's assessment			
No. of subjects with CR, PR, or SD ≥24 weeks (n)	3	37	40
Clinical benefit rate (%)	50.0	48.7	48.8
Exact 95% CI for clinical benefit rate	11.8, 88.2	37.0, 60.4	37.6, 60.1
Independent assessment			
No. of subjects with CR, PR, or SD ≥24 weeks (n)	2	30	32
Clinical benefit rate (%)	33.3	39.5	39.0
Exact 95% CI for clinical benefit rate	4.3, 77.7	28.4, 51.4	28.4, 50.4

Abbreviations: CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number; PR = partial response; SD = stable disease.

Secondary Endpoint Results:

Progression-Free Survival

Table 9 summarizes PFS in the ITT population. PFS is the interval from the date of enrollment until the earlier date of progression or death, censored at the last tumor evaluation date.

The median PFS was 7.3 months (95% CI: 4.0 to 10.0) according to the Investigator's assessment. The median PFS according to the independent assessment was 5.4 months (95% CI: 3.6 to 7.2).

Table 9. Progression-Free Survival, ITT Population

	Treatment		
Progression-Free Survival	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Investigator's assessment			
No. of subjects with post-baseline tumor assessment (n, %)	6 (100)	72 (94.7)	78 (95.1)
No. of subjects with disease progression or who died (n, %)	5 (83.3)	68 (89.5)	73 (89.0)
No. of censored subjects (n, %)	1 (16.7)	8 (10.5)	9 (11.0)
Median PFS in months	8.7	7.3	7.3
95% CI for median PFS	4.0, 29.0	3.8, 9.9	4.0, 10.0
Independent assessment			
No. of subjects with post-baseline tumor assessment (n, %)	6 (100)	72 (94.7)	78 (95.1)
No. of subjects with disease progression or who died (n, %)	6 (100)	70 (92.1)	76 (92.7)
No. of censored subjects (n, %)	0	6 (7.9)	6 (7.3)
Median PFS in months	4.8	5.4	5.4
95% CI for median PFS	1.9, 20.3	3.6, 7.2	3.6, 7.2

Abbreviations: CI = confidence interval; ITT = intent-to-treat; NA = not available; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number; PFS = progression-free survival.

Objective Response Rate

Table 10 shows the ORRs for the ITT population. Objective response was defined as the percentage of subjects who achieved CR or PR, however, no subject had a CR in this study. According to the Investigator's assessment objective response (ie, PR) was observed in 9 of 82 subjects and the ORR was 11.0% (95% CI: 5.1% to 19.8%). The objective response according to the independent assessment was observed in 3 of 82 subjects and the ORR was 3.7% (95% CI: 0.8% to 10.3%).

Table 10. Objective Response Rate, ITT Population

	Treatment		
Objective response rate	**Group A ($20 mg/m^2$) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Investigator's assessment			
No. of subjects with CR or PR (n)	0	9	9
Objective response rate (%)	-	11.8	11.0
Exact 95% CI for objective response rate	-	5.6, 21.3	5.1, 19.8
Independent assessment			
No. of subjects with CR or PR (n)	0	3	3
Objective response rate (%)	-	3.9	3.7
Exact 95% CI for objective response rate	-	0.8, 11.1	0.8, 10.3

Abbreviations: CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number; PR = partial response.

Duration of Objective Response

Table 11 shows the duration of objective response for the ITT population. The duration of objective response was measured from the time at which measurement criteria were met for CR or PR (whichever status was recorded first) until the first date on which recurrence or PD was objectively documented, taking as the reference for PD the smallest sum of the LDs recorded since enrollment. This parameter applied only to subjects with objective response.

The median duration of objective response were 31.3 months (95% CI: 4.5 to not available) and 12.5 months (95% CI: 3.7 to 21.3) according to the Investigator's assessment and the independent assessment, respectively.

The duration of objective response for the evaluable population was similar to that of ITT population.

Table 11. Duration of Objective Response, ITT Population

	Treatment		
Duration of Objective Response	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
Investigator's assessment			
No. of subjects with objective response (n,%)	0	9 (11.8)	9 (11.0)
No. of subjects with PD (n,%)	0	4 (5.3)	4 (4.9)
No. of censored subjects (n,%)	0	5 (6.6)	5 (6.1)
Median duration in months	NA	31.3	31.3
95% CI for median duration	NA, NA	4.5, NA	4.5, NA
Independent assessment			
No. of subjects with objective response (n,%)	0	3 (3.9)	3 (3.7)
No. of subjects with PD (n,%)	0	2 (2.6)	2 (2.4)
No. of censored subjects (n,%)	0	1 (1.3)	1 (1.2)
Median duration in months	NA	12.5	12.5
95% CI for median duration	NA, NA	3.7, 21.3	3.7, 21.3

Abbreviations: CI = confidence interval; ITT = intent-to-treat; NA = not available; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria;No. = number; PD = progressive disease.

Time to Treatment Failure

Table 12 shows the TTF for the ITT population. The TTF is the interval from the date of enrollment until the earlier date of progression or death (any cause), withdrawal from treatment owing to AE, subject refusal, loss to follow-up (censored at the last contact date), or further anticancer therapy before documented progression (whichever occurred first). The median TTF was 5.4 months (95% CI: 3.5 to 7.4).

Table 12. Time to Treatment Failure, ITT Population

	Treatment		
Time to Treatment Failure	**Group A (20 mg/m^2) (N=6)**	**Group B (25 mg/body) (N=76)**	**Total (N=82)**
No. of subjects with post-baseline tumor assessment (n, %)	6 (100)	72 (94.7)	78 (95.1)
No. of subjects with treatment failures (n, %)	6 (100)	76 (100)	82 (100)
No. of censored subjects (n, %)	0	0	0
Median TTF in months	7.7	5.4	5.4
95% CI for median TTF	1.9, 29.0	3.5, 7.4	3.5, 7.4

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number; TTF = time to treatment failure.

Overall Survival

Table 13 shows the OS for the ITT population. The OS was measured from the date of enrollment until the date of death, censored at the last date on which the subject was known to be alive.

A total of 59 subjects (72.0%) died and 23 subjects (28.0%) were censored. The median OS was 18.3 months (95% CI: 13.5 to 26.1).

Table 13. Overall Survival, ITT Population

Overall Survival	Treatment		
	Group A (20 mg/m^2) (N=6)	Group B (25 mg/body) (N=76)	Total (N=82)
No. of deaths (n,%)	5 (83.3)	54 (71.1)	59 (72.0)
No. of censored subjects (n,%)	1 (16.7)	22 (28.9)	23 (28.0)
Median OS in months	29.1	17.8	18.3
95% CI for median OS	4.4, 36.3	13.5, 25.3	13.5, 26.1

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number; OS = overall survival.

Safety Results:

Table 14 shows the all causalities treatment emergent AEs (TEAEs) having a frequency rate >5% in the temsirolimus 20 mg/m^2 treatment group and temsirolimus 25 mg/body treatment group. The table presents the number of occurrences of treatment emergent all causalities AEs (n1) and the number of occurrences of treatment emergent causally related to treatment AEs (n2).

All causalities TEAEs reported in more than 30% of total subjects were rash, stomatitis, hypercholesterolemia and decreased appetite, hypertriglyceridemia, pyrexia, hypophosphatemia and hyperglycemia, anemia, fatigue, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased.

The most frequently observed all causalities TEAEs (>60%) in Group A were rash, anemia, stomatitis, ALT increased, AST increased, weight decreased, diarrhea, blood alkaline phosphatase increased, prothrombin time prolonged, and nail disorder.

Drug-related TEAEs were those assessed by the Investigator to be associated, definitely related, probably related, possibly related, or of unknown or undetermined relationship to temsirolimus treatment.

The frequently observed drug-related TEAEs were rash, stomatitis, hypercholesterolemia, hypertriglyceridemia, decreased appetite, hyperglycemia, ALT increased, and AST increased.

Table 14. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
System Organ Class[a] **Preferred Term**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Number (%) of subjects:						
Evaluable for adverse events	6			76		
With adverse events	6 (100.0)			76 (100.0)		
Blood and lymphatic system disorders	5 (83.3)	43	39	35 (46.1)	207	156
Anaemia	5 (83.3)	19	15	23 (30.3)	139	108
Leukopenia	2 (33.3)	4	4	7 (9.2)	15	11
Lymphopenia	2 (33.3)	8	8	9 (11.8)	18	7
Neutropenia	2 (33.3)	2	2	3 (3.9)	4	4
Thrombocytopenia	1 (16.7)	10	10	9 (11.8)	31	26
Cardiac disorders	3 (50.0)	5	5	1 (1.3)	3	3
Cardiac valve disease	1 (16.7)	1	1	0	0	0
Pericardial effusion	1 (16.7)	1	1	0	0	0
Tachycardia	2 (33.3)	3	3	1 (1.3)	3	3
Ear and labyrinth disorders	1 (16.7)	1	1	0	0	0
Otorrhoea	1 (16.7)	1	1	0	0	0
Eye disorders	1 (16.7)	3	1	0	0	0
Cataract subcapsular	1 (16.7)	2	0	0	0	0
Conjunctival hyperaemia	1 (16.7)	1	1	0	0	0
Gastrointestinal disorders	6 100.0)	58	41	67 (88.2)	461	374
Abdominal discomfort	1 (16.7)	1	1	9 (11.8)	17	8
Abdominal distension	0	0	0	6 (7.9)	8	5
Abdominal pain	0	0	0	9 (11.8)	23	8
Anorectal discomfort	0	0	0	4 (5.3)	10	10
Breath odour	1 (16.7)	1	1	0	0	0
Cheilitis	2 (33.3)	5	5	4 (5.3)	6	5
Constipation	3 (50.0)	9	4	17 (22.4)	37	10
Dental caries	1 (16.7)	1	0	2 (2.6)	4	3
Diarrhoea	4 (66.7)	9	4	17 (22.4)	31	25
Faeces discoloured	1 (16.7)	1	1	0	0	0
Gastritis	1 (16.7)	5	5	1 (1.3)	1	0
Mouth ulceration	0	0	0	9 (11.8)	32	32
Nausea	0	0	0	18 (23.7)	41	35
Periodontitis	1 (16.7)	3	0	4 (5.3)	10	2
Stomatitis	5 (83.3)	16	16	42 (55.3)	215	213
Toothache	2 (33.3)	4	2	1 (1.3)	3	3
Vomiting	3 (50.0)	3	2	11 (14.5)	23	15
General disorders and administration site conditions	6 (100.0)	204	196	62 (81.6)	271	191
Asthenia	0	0	0	11 (14.5)	23	17
Axillary pain	1 (16.7)	1	1	0	0	0
Chest discomfort	0	0	0	6 (7.9)	12	9
Chills	1 (16.7)	1	1	6 (7.9)	16	15
Face oedema	1 (16.7)	7	7	9 (11.8)	17	14
Fatigue	3 (50.0)	12	12	26 (34.2)	64	49
General physical health deterioration	2 (33.3)	4	0	2 (2.6)	2	1
Influenza like illness	0	0	0	5 (6.6)	12	12
Malaise	1 (16.7)	149	149	1 (1.3)	2	0

Table 14. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
System Organ Class[a] **Preferred Term**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Mucosal inflammation	0	0	0	4 (5.3)	8	8
Oedema	1 (16.7)	8	8	3 (3.9)	4	4
Oedema peripheral	1 (16.7)	9	9	13 (17.1)	26	10
Pyrexia	3 (50.0)	13	9	30 (39.5)	85	52
Infections and infestations	4 (66.7)	27	17	35 (46.1)	140	80
Adenoviral conjunctivitis	1 (16.7)	2	2	0	0	0
Bronchitis	1 (16.7)	1	1	2 (2.6)	4	0
Cellulitis	1 (16.7)	2	2	1 (1.3)	2	2
Nail infection	1 (16.7)	5	5	1 (1.3)	1	1
Nasopharyngitis	1 (16.7)	11	1	7 (9.2)	15	4
Otitis media	1 (16.7)	2	2	1 (1.3)	1	0
Paronychia	0	0	0	8 (10.5)	29	29
Pneumonia	1 (16.7)	1	1	5 (6.6)	10	10
Sinusitis	1 (16.7)	1	1	2 (2.6)	3	3
Sputum purulent	1 (16.7)	1	1	0	0	0
Upper respiratory tract infection	0	0	0	20 (26.3)	73	30
Urinary tract infection	1 (16.7)	1	1	2 (2.6)	2	1
Injury, poisoning and procedural complications	4 (66.7)	7	1	2 (2.6)	4	0
Excoriation	2 (33.3)	2	0	1 (1.3)	2	0
Head injury	1 (16.7)	1	0	0	0	0
Mouth injury	1 (16.7)	1	0	0	0	0
Post procedural complication	1 (16.7)	1	1	0	0	0
Wound complication	1 (16.7)	2	0	1 (1.3)	2	0
Investigations	6 (100.0)	284	267	61 (80.3)	1048	916
Activated partial thromboplastin time prolonged	1 (16.7)	3	3	2 (2.6)	4	2
Alanine aminotransferase increased	5 (83.3)	9	9	23 (30.3)	89	85
Aspartate aminotransferase increased	5 (83.3)	19	19	23 (30.3)	80	74
Blood albumin decreased	3 (50.0)	19	14	3 (3.9)	10	9
Blood alkaline phosphatase increased	4 (66.7)	13	13	14 (18.4)	32	15
Blood calcium decreased	2 (33.3)	7	7	3 (3.9)	9	8
Blood cholesterol increased	2 (33.3)	21	21	12 (15.8)	52	52
Blood creatine increased	0	0	0	4 (5.3)	7	6
Blood creatinine	0	0	0	4 (5.3)	7	7
Blood creatinine increased	2 (33.3)	12	12	24 (31.6)	63	43
Blood glucose increased	0	0	0	9 (11.8)	64	63
Blood iron decreased	1 (16.7)	2	2	0	0	0
Blood lactate dehydrogenase increased	3 (50.0)	8	8	15 (19.7)	37	35
Blood magnesium increased	1 (16.7)	2	2	0	0	0
Blood phosphorus decreased	1 (16.7)	1	1	2 (2.6)	10	10
Blood potassium decreased	1 (16.7)	6	6	2 (2.6)	4	0
Blood potassium increased	1 (16.7)	12	12	2 (2.6)	7	1
Blood sodium decreased	1 (16.7)	7	0	2 (2.6)	5	0
Blood triglycerides increased	3 (50.0)	12	12	15 (19.7)	125	124
Blood urea increased	0	0	0	6 (7.9)	11	7
C-reactive protein increased	2 (33.3)	5	5	2 (2.6)	5	5
Gamma-glutamyltransferase increased	3 (50.0)	12	12	7 (9.2)	33	29

Table 14. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
System Organ Class[a] **Preferred Term**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Glycosylated haemoglobin increased	2 (33.3)	3	3	9 (11.8)	13	7
Haematocrit decreased	0	0	0	10 (13.2)	44	42
Haemoglobin decreased	1 (16.7)	22	22	22 (28.9)	98	82
Laboratory test abnormal	1 (16.7)	1	1	0	0	0
Neutrophil count decreased	0	0	0	6 (7.9)	20	16
Neutrophil count increased	1 (16.7)	1	1	1 (1.3)	2	0
Platelet count decreased	3 (50.0)	33	33	18 (23.7)	75	75
Platelet count increased	1 (16.7)	1	1	4 (5.3)	7	4
Protein total decreased	1 (16.7)	1	1	1 (1.3)	9	9
Protein total increased	1 (16.7)	2	2	5 (6.6)	9	3
Prothrombin time prolonged	4 (66.7)	18	18	0	0	0
Red blood cell count decreased	0	0	0	4 (5.3)	8	6
Weight decreased	5 (83.3)	31	26	18 (23.7)	46	43
Weight increased	0	0	0	4 (5.3)	5	3
White blood cell count decreased	0	0	0	14 (18.4)	54	51
White blood cell count increased	1 (16.7)	1	1	3 (3.9)	4	0
Metabolism and nutrition disorders	6 (100.0)	101	99	62 (81.6)	859	737
Decreased appetite	1 (16.7)	1	1	36 (47.4)	92	73
Diabetes mellitus	3 (50.0)	16	16	2 (2.6)	5	5
Hypercalcaemia	0	0	0	6 (7.9)	14	4
Hypercholesterolaemia	2 (33.3)	16	16	34 (44.7)	198	195
Hyperglycaemia	3 (50.0)	14	14	28 (36.8)	140	117
Hyperkalaemia	1 (16.7)	1	0	4 (5.3)	12	6
Hyperlipidaemia	0	0	0	4 (5.3)	8	8
Hypermagnesaemia	0	0	0	8 (10.5)	16	15
Hypertriglyceridaemia	2 (33.3)	20	20	32 (42.1)	154	149
Hypoalbuminaemia	0	0	0	6 (7.9)	16	6
Hypocalcaemia	1 (16.7)	8	8	13 (17.1)	65	58
Hypokalaemia	1 (16.7)	1	1	8 (10.5)	15	14
Hyponatraemia	1 (16.7)	1	1	8 (10.5)	21	4
Hypophosphataemia	3 (50.0)	23	22	28 (36.8)	103	83
Musculoskeletal and connective tissue disorders	4 (66.7)	21	10	25 (32.9)	82	44
Arthralgia	0	0	0	9 (11.8)	23	18
Back pain	3 (50.0)	14	5	8 (10.5)	15	2
Flank pain	0	0	0	5 (6.6)	8	2
Musculoskeletal discomfort	1 (16.7)	2	2	2 (2.6)	4	0
Musculoskeletal pain	1 (16.7)	3	1	3 (3.9)	5	2
Musculoskeletal stiffness	1 (16.7)	2	2	0	0	0
Myalgia	0	0	0	11 (14.5)	27	20
Nervous system disorders	5 (83.3)	13	13	15 (19.7)	34	28
Dizziness	0	0	0	5 (6.6)	9	8
Dysgeusia	3 (50.0)	5	5	7 (9.2)	10	9
Headache	1 (16.7)	1	1	6 (7.9)	15	11
Neuropathy peripheral	3 (50.0)	4	4	0	0	0
Parosmia	1 (16.7)	3	3	0	0	0
Psychiatric disorders	0	0	0	8 (10.5)	15	5
Insomnia	0	0	0	8 (10.5)	15	5

Table 14. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
System Organ Class[a] **Preferred Term**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Renal and urinary disorders	2 (33.3)	49	49	4 (5.3)	6	0
Pollakiuria	1 (16.7)	2	2	3 (3.9)	4	0
Proteinuria	1 (16.7)	47	47	1 (1.3)	2	0
Reproductive system and breast disorders	0	0	0	4 (5.3)	17	0
Pelvic pain	0	0	0	4 (5.3)	17	0
Respiratory, thoracic and mediastinal disorders	6 (100.0)	83	80	50 (65.8)	258	185
Cough	2 (33.3)	5	5	20 (26.3)	51	32
Dyspnoea	0	0	0	16 (21.1)	36	14
Dyspnoea exertional	1 (16.7)	2	2	5 (6.6)	12	10
Epistaxis	3 (50.0)	46	46	15 (19.7)	47	39
Haemoptysis	0	0	0	9 (11.8)	14	5
Hypoxia	1 (16.7)	2	2	2 (2.6)	6	6
Interstitial lung disease	3 (50.0)	10	10	12 (15.8)	48	44
Lower respiratory tract inflammation	1 (16.7)	1	1	0	0	0
Nasal dryness	1 (16.7)	1	0	0	0	0
Oropharyngeal pain	1 (16.7)	2	1	10 (13.2)	18	15
Pleural effusion	1 (16.7)	1	1	4 (5.3)	6	6
Productive cough	0	0	0	7 (9.2)	18	12
Pulmonary hypertension	3 (50.0)	5	5	0	0	0
Rhinorrhoea	3 (50.0)	7	7	1 (1.3)	1	1
Upper respiratory tract inflammation	1 (16.7)	1	0	1 (1.3)	1	1
Skin and subcutaneous tissue disorders	6 (100.0)	55	53	51 (67.1)	306	288
Acne	2 (33.3)	6	6	3 (3.9)	6	6
Alopecia	1 (16.7)	1	1	0	0	0
Dermatitis	1 (16.7)	2	2	1 (1.3)	4	4
Dermatitis acneiform	0	0	0	4 (5.3)	4	4
Dry skin	1 (16.7)	3	3	2 (2.6)	2	2
Exfoliative rash	0	0	0	4 (5.3)	4	4
Nail disorder	4 (66.7)	9	9	20 (26.3)	36	36
Palmar-plantar erythrodysaesthesia syndrome	2 (33.3)	4	4	7 (9.2)	12	10
Pruritus	1 (16.7)	1	1	23 (30.3)	57	50
Rash	6 (100.0)	18	18	43 (56.6)	168	163
Seborrhoeic dermatitis	1 (16.7)	5	3	0	0	0
Skin exfoliation	0	0	0	6 (7.9)	10	6
Skin hyperpigmentation	2 (33.3)	5	5	1 (1.3)	1	1
Skin reaction	1 (16.7)	1	1	1 (1.3)	2	2
Vascular disorders	2 (33.3)	7	7	13 (17.1)	25	22
Hot flush	2 (33.3)	3	3	0	0	0
Hypertension	0	0	0	11 (14.5)	23	20
Phlebitis	1 (16.7)	4	4	2 (2.6)	2	2

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
Abbreviations: n = number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1 = number of occurrences of treatment-emergent all causalities adverse events; n2 = number of occurrences of treatment-emergent causally related to treatment adverse events; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0).
a. MedDRA (v15.0) coding dictionary applied

Table 15 shows the all treatment-emergent SAEs by system organ class in the temsirolimus 20 mg/m^2 and temsirolimus 25 mg/body treatment groups. The table presents the number of occurrences of treatment-emergent all causalities AEs (n1) and the number of occurrences of treatment-emergent causally related to treatment AEs (n2).

A total of 32 subjects (39.0%) reported SAEs during this study. The most frequently observed SAEs (more than 5%) were pneumonia and interstitial lung disease (ILD).

Table 15. Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term

System Organ Class[a] Preferred Term	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:						
Evaluable for adverse events	6			76		
With adverse events	4 (66.7)			28 (36.8)		
Cardiac disorders	1 (16.7)	1	1	1 (1.3)	1	0
Palpitations	0	0	0	1 (1.3)	1	0
Pericardial effusion	1 (16.7)	1	1	0	0	0
Eye disorders	1 (16.7)	4	0	0	0	0
Cataract subcapsular	1 (16.7)	4	0	0	0	0
Gastrointestinal disorders	0	0	0	7 (9.2)	20	14
Abdominal distension	0	0	0	1 (1.3)	3	3
Abdominal hernia	0	0	0	1 (1.3)	2	0
Abdominal pain	0	0	0	2 (2.6)	4	3
Diarrhoea	0	0	0	2 (2.6)	2	2
Faecal incontinence	0	0	0	1 (1.3)	1	0
Peritoneal haemorrhage	0	0	0	1 (1.3)	2	0
Small intestinal haemorrhage	0	0	0	1 (1.3)	5	5
Small intestinal perforation	0	0	0	1 (1.3)	1	1
General disorders and administration site conditions	1 (16.7)	2	0	3 (3.9)	5	1
Asthenia	0	0	0	1 (1.3)	2	0
General physical health deterioration	1 (16.7)	2	0	0	0	0
Pyrexia	0	0	0	2 (2.6)	3	1
Hepatobiliary disorders	0	0	0	1 (1.3)	1	0
Hepatic failure	0	0	0	1 (1.3)	1	0
Infections and infestations	2 (33.3)	7	7	12 (15.8)	36	11
Anal abscess	0	0	0	1 (1.3)	1	0
Bronchopneumonia	0	0	0	1 (1.3)	2	0
Cellulitis	1 (16.7)	2	2	0	0	0
Lung infection	0	0	0	2 (2.6)	4	2
Peritonitis	0	0	0	1 (1.3)	2	2
Pneumonia	1 (16.7)	5	5	6 (7.9)	16	5
Postoperative wound infection	0	0	0	1 (1.3)	2	0
Sepsis	0	0	0	1 (1.3)	4	0
Tonsillitis	0	0	0	1 (1.3)	1	0
Urinary tract infection	0	0	0	2 (2.6)	4	2
Injury, poisoning and procedural complications	0	0	0	1 (1.3)	2	0
Wound complication	0	0	0	1 (1.3)	2	0
Investigations	0	0	0	1 (1.3)	4	0

Table 15. Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term

System Organ Class[a] Preferred Term	Group A (Temsirolimus 20 mg/m^2)			Group B (Temsirolimus 25 mg/body)		
	n (%)	n1	n2	n (%)	n1	n2
Blood creatinine increased	0	0	0	1 (1.3)	4	0
Metabolism and nutrition disorders	0	0	0	1 (1.3)	3	0
Hyperglycaemia	0	0	0	1 (1.3)	3	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (1.3)	2	0
Muscular weakness	0	0	0	1 (1.3)	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	3 (3.9)	5	0
Renal cell carcinoma	0	0	0	1 (1.3)	1	0
Tumour embolism	0	0	0	1 (1.3)	3	0
Tumour pain	0	0	0	1 (1.3)	1	0
Nervous system disorders	0	0	0	3 (3.9)	3	1
Cerebral haemorrhage	0	0	0	1 (1.3)	1	1
Paraplegia	0	0	0	1 (1.3)	1	0
Spinal cord compression	0	0	0	1 (1.3)	1	0
Psychiatric disorders	0	0	0	2 (2.6)	2	0
Completed suicide	0	0	0	1 (1.3)	1	0
Delirium	0	0	0	1 (1.3)	1	0
Renal and urinary disorders	0	0	0	3 (3.9)	8	0
Azotaemia	0	0	0	1 (1.3)	3	0
Haematuria	0	0	0	1 (1.3)	1	0
Renal failure	0	0	0	1 (1.3)	1	0
Renal failure acute	0	0	0	1 (1.3)	2	0
Renal impairment	0	0	0	1 (1.3)	1	0
Respiratory, thoracic and mediastinal disorders	2 (33.3)	5	5	10 (13.2)	30	25
Atelectasis	0	0	0	1 (1.3)	3	3
Cough	0	0	0	1 (1.3)	1	1
Dyspnoea	0	0	0	2 (2.6)	2	0
Haemoptysis	0	0	0	1 (1.3)	1	0
Interstitial lung disease	2 (33.3)	5	5	4 (5.3)	13	13
Pleural effusion	0	0	0	2 (2.6)	8	8
Respiratory failure	0	0	0	2 (2.6)	2	0
Vascular disorders	0	0	0	1 (1.3)	1	0
Circulatory collapse	0	0	0	1 (1.3)	1	0

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator
Abbreviations: n = number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1 = number of occurrences of treatment-emergent all causalities adverse events; n2 = number of occurrences of treatment-emergent causally related to treatment adverse events; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0).
a. MedDRA (v15.0) coding dictionary applied

Permanent Discontinuations Due to Adverse Events

AEs were cause for discontinuation of treatment for 27 subjects (32.9%). Table 16 summarizes by system organ class the AEs that were cited as causing premature subject discontinuation. The most frequent causes for discontinuation of treatment was ILD (8 subjects, 9.8%) followed by pneumonia (5 subjects, 6.1%).

Table 16. Number (%) of Subjects Reporting Adverse Events, Adverse Events Leading to Treatment Discontinuation, Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Group A (Temsirolimus 20 mg/m^2) (n, %)	Group B (Temsirolimus 25 mg/body) (n, %)	Total (n, %)
Total number of subjects that participated in study (N)	6	76	82
Any adverse event	4 (66.7)	23 (30.3)	27 (32.9)
General disorders and administration site conditions	1 (16.7)	1 (1.3)	2 (2.4)
Fatigue	0	1 (1.3)	1 (1.2)
General physical health deterioration	1 (16.7)	0	1 (1.2)
Hepatobiliary disorders	0	1 (1.3)	1 (1.2)
Hepatic failure	0	1 (1.3)	1 (1.2)
Infections and infestations	0	8 (10.5)	8 (9.8)
Lung infection	0	2 (2.6)	2 (2.4)
Pneumonia	0	5 (6.6)	5 (6.1)
Sepsis	0	1 (1.3)	1 (1.2)
Urinary tract infection	0	2 (2.6)	2 (2.4)
Investigations	0	1 (1.3)	1 (1.2)
Carbon monoxide diffusing capacity decreased	0	1 (1.3)	1 (1.2)
Metabolism and nutrition disorders	0	1 (1.3)	1 (1.2)
Hyperglycaemia	0	1 (1.3)	1 (1.2)
Nervous system disorders	0	1 (1.3)	1 (1.2)
Spinal cord compression	0	1 (1.3)	1 (1.2)
Psychiatric disorders	0	1 (1.3)	1 (1.2)
Completed suicide	0	1 (1.3)	1 (1.2)
Renal and urinary disorders	0	2 (2.6)	2 (2.4)
Renal failure	0	1 (1.3)	1 (1.2)
Renal failure acute	0	1 (1.3)	1 (1.2)
Renal impairment	0	1 (1.3)	1 (1.2)
Respiratory, thoracic and mediastinal disorders	3 (50.0)	9 (11.8)	12 (14.6)
Haemoptysis	0	1 (1.3)	1 (1.2)
Hypoxia	1 (16.7)	1 (1.3)	2 (2.4)
Interstitial lung disease	2 (33.3)	6 (7.9)	8 (9.8)
Respiratory failure	0	1 (1.3)	1 (1.2)
Skin and subcutaneous tissue disorders	0	1 (1.3)	1 (1.2)
Rash	0	1 (1.3)	1 (1.2)
Vascular disorders	0	1 (1.3)	1 (1.2)
Circulatory collapse	0	1 (1.3)	1 (1.2)

Table 16. Number (%) of Subjects Reporting Adverse Events, Adverse Events Leading to Treatment Discontinuation, Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Group A (Temsirolimus 20 mg/m^2) (n, %)	Group B (Temsirolimus 25 mg/body) (n, %)	Total (n, %)

Events leading to treatment discontinuation determined using action code of D or W.
Classifications of adverse events were based on the MedDRA.
Abbreviations: D =discontinuation; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; MedDRA = Medical Dictionary for Regulatory Activities; W = withdrawal.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject might report 2 or more different adverse events within the higher level category.

Dose Reductions or Temporary Discontinuations due to Adverse Events:

A total of 26 subjects (31.7%) had at least 1 dose reduction. The AE most commonly causing dose reductions was ILD.

A total of 49 subjects (59.8%) had at least 1 dose delay. The most common causes of dose delay were ILD, stomatitis, rash, pyrexia, and ALT increased.

Deaths:

Table 17 shows the summary of deaths for the ITT population. A total of 59 subjects (72.0%) died during this study. The most common cause of death was disease progression, in 45 of 59 subjects. Eight (8) subjects died of AEs, including 2 subjects who died more than 30 days after the last study drug administration. Two (2) of the 8 AEs resulted in death were drug related. The reasons for the deaths of 2 subjects were reported as unknown or not clear. Five (5) subjects (6.1%) died within 15 days of the last dose.

Table 17. Summary of Deaths, ITT Population

	Treatment		
Deaths (n,%)	Group A (Temsirolimus 20 mg/m^2) (N=6)	Group B (Temsirolimus 25 mg/body) (N=76)	Total (N=82)
No. of all deaths	5 (83.3)	54 (71.1)	59 (72.0)
No. of deaths within 15 days post last dose	0	5 (6.6)	5 (6.1)
No. of deaths after 15 days post last dose	5 (83.3)	49 (64.5)	54 (65.9)
Reason for death[a]			
Disease progression	5 (100)	40 (74.1)	45 (76.3)
Adverse Event	0	8 (14.8)	8 (13.6)
Other	0	6 (11.1)	6 (10.2)

Abbreviation: ITT = intent-to-treat; N = total number of subjects that participated in clinical study; n = number of subjects meeting prespecified criteria; No. = number.
a. Percentages are based on number of subjects who died in each treatment group.

CONCLUSION: Temsirolimus at 20 mg/m^2 and 25 mg (flat dose) was well tolerated in Japanese, Korean, and Chinese subjects with advanced RCC. Overall, temsirolimus given as a 25-mg flat dose has demonstrated an acceptable safety profile and promising efficacy in East Asian subjects with advanced RCC.