CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-088

MEDICAL REVIEW

May 30, 2007

Office Director Memo

Richard Pazdur, MD
Office of Oncology Drug Products

Drug: TORISEL (TEMSIROLIMUS)
RECOMMENDED REGULATORY ACTION: APPROVAL (REGULAR APPROVAL)

Summary of Clinical Data Package:

Indication: TORISEL IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA.

Efficacy and safety were demonstrated at a second interim analysis of a phase 3, multi-center, international, randomized, open-label study in previously untreated patients with advanced renal cell carcinoma (RCC) who had 3 or more of 6 poor prognostic factors. These factors included time of diagnosis to randomization of less than one year, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, and/or more than one metastatic organ site.

Six hundred and twenty six patients were randomized to one of three arms: Interferon alfa (IFN) alone (n=207), temsirolimus 25 mg alone (n=209), or the combination of temsirolimus 15 mg and IFN-α (n=210). Patients were stratified for prior nephrectomy and geographic region. Sixty-nine percent were less than 65 years old and 68% were male. Temsirolimus was infused intravenously over 30-60 minutes once a week either until disease progression or unacceptable toxicity. Premedication with an antihistamine (e.g., diphenhydramine) was recommended.

Single-agent temsirolimus was associated with a statistically significant improvement in overall survival (OS) when compared to IFN (hazard ratio 0.73 [95% CI: 0.58, 0.92]; p value: 0.0078). The median OS was 10.9 months on the temsirolimus arm and 7.3 months on the IFN arm. Progression-free survival (PFS) was a secondary endpoint and the median PFS was 5.5 months on the temsirolimus arm and arm [hazard ratio 0.66 (95% CI: 0.53, 0.81)].3.1 months on the IFN.The combination of Temsirolimus 15 mg and IFN alone did not result in a significant increase in OS when compared with IFN and was associated with an increase in multiple adverse reactions.

The most common adverse reactions (incidence ≥ 30%) were rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) were anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, hypocalcemia, elevated AST, and leukopenia.

The most common grade 3/4 adverse reactions (incidence ≥ 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence ≥ 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.

Rare serious adverse reactions associated with temsirolimus included interstitial lung disease, bowel perforation, and acute renal failure.

Past regulatory actions in renal cell carcinoma.

In 1992, IL- 2 was approved based on 255 metastatic RCC patients treated with IL-2 in 7 clinical studies conducted in 21 institutions. Approval was based on a 15% response rate with 7% CR with approximately 80 months median duration and 8% PR with 20 month median duration, In December 2005, sorafenib (Nexavar) was approved for advanced renal cell carcinoma based on the demonstration of an improved PFS in a large, multinational, randomized double-blind, placebo-controlled phase 3 study. The median PFS was 167 days in the sorafenib group versus 84 days in the placebo group (log rank $p < 0.000001$).

In January, 2006, sunitinib (Sutent) received accelerated approval for the treatment of advanced renal cell carcinoma based on partial response rates and response durations. (25% partial response rate in one study and a 36.5% partial response rate with median duration of 54 weeks.)This accelerated approval of sunitinib was converted to regular approval in February, 2007 based on an improvement in PFS in a randomized study comparing sunitinib to IFN. In this 750 patient study of treatment-naïve metastatic renal cell carcinoma, the median PFS was 47 weeks for sunitinib- treated patients and 22 weeks for the INF-treated patients (HR = 0.415, (5% CI .320, .530, $p<0.00001$. Objective response rates were 27.5% (sunitinib) and 5.3% (IFN.)

Recommendation

I concur with the Division of Oncology Drug Products (Justice, Kwitkowski, Prowell reviews) in granting regular approval to this New Drug Application for advanced renal cell carcinoma. This drug is the first drug to demonstrate an improvement in overall survival and is accompanied by an improvement in PFS. The risk benefit analysis is consistent with prior approvals for the treatment of advanced malignancies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
5/30/2007 03:50:43 PM
MEDICAL OFFICER

Division Director Summary Review of a New Drug Application

NDA: 22-088
Drug: TORISEL™ Kit (temsirolimus) injection for intravenous infusion
Applicant: Wyeth Pharmaceuticals Inc.
Date: May 30, 2007

This new drug application seeks approval of TORISEL for the treatment of advanced renal cell carcinoma. Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In *in vitro* studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

The safety and efficacy of TORISEL is based on a single study which is described below in excerpts from the draft labeling.

> A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving TORISEL or TORISEL plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n=207), TORISEL alone (25 mg weekly; n=209), or the combination arm (n=210).
>
> The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

The median duration of treatment in the TORISEL arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks).

There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL 25 mg arm compared to IFN-α. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in overall survival when compared with IFN-α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 3.

Treatment with the combination of TORISEL 15 mg and IFN-α was associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in overall survival when compared with IFN-α alone.

Figure 1: Kaplan–Meier Curves for Overall Survival – TORISEL vs. IFN

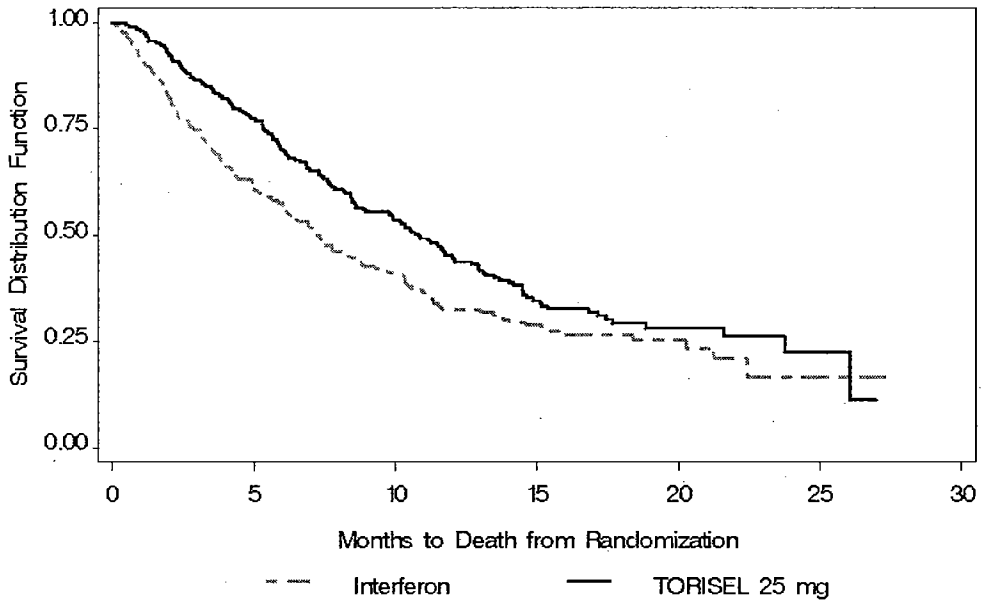


Table 3: Summary of Efficacy Results of TORISEL vs. IFN-α				
Parameter	**TORISEL** n = 209	**IFN-α** n = 207	**P-value[a]**	**Hazard Ratio (95% CI)[b]**
Median Overall Survival Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0078*	0.73 (0.58, 0.92)
Median Progression-Free Survival Months (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	0.0001**	0.66 (0.53, 0.81)
Overall Response Rate % (95% CI)	8.6 (4.8, 12.4)	4.8 (1.9, 7.8)	0.1232**[c]	NA

CI = confidence interval; NA = not applicable

* A comparison is considered statistically significant if the p-value is <0.0159 (O'Brien-Fleming boundary at 446 deaths).

** Not adjusted for multiple comparisons.

a. Based on log-rank test stratified by prior nephrectomy and region.

b. Based on Cox proportional hazard model stratified by prior nephrectomy and region.

c. Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

The most common (≥ 30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥ 30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and neutropenia.

Table 1 shows the percentage of patients experiencing treatment emergent adverse reactions. Reactions reported in at least 10% of patients who received TORISEL 25 mg alone or IFN-α alone are listed. Table 2 shows the percentage of patients experiencing selected laboratory abnormalities. Data for the same adverse reactions and laboratory abnormalities in the IFN-α alone arm are shown for comparison.

Table 1 –Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial.				
Adverse Reaction	**TORISEL 25 mg n=208**		**IFN-α n=200**	
	All Grades* n (%)	**Grades 3&4* n (%)**	**All Grades* n (%)**	**Grades 3&4* n (%)**
Any	208 (100)	139 (67)	199 (100)	155 (78)
General disorders				
Asthenia	104 (50)	21 (10)	125 (63)	52 (26)
Edema[a]	73 (35)	7 (3)	21 (11)	1 (1)
Pain	59 (28)	10 (5)	31 (16)	4 (2)
Pyrexia	50 (24)	1 (1)	99 (50)	7 (4)
Weight Loss	39 (19)	3 (1)	49 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest Pain	34 (16)	2 (1)	18 (9)	2 (1)
Chills	17 (8)	1(1)	59 (30)	3 (2)
Gastrointestinal disorders				
Mucositis[b]	86 (41)	6 (3)	19 (10)	0 (0)
Anorexia	66 (32)	6 (3)	87 (44)	8 (4)
Nausea	77 (37)	5 (2)	82 (41)	9 (5)
Diarrhea	56 (27)	3 (1)	40 (20)	4 (2)
Abdominal Pain	44 (21)	9 (4)	34 (17)	3 (2)
Constipation	42 (20)	0 (0)	36 (18)	1 (1)
Vomiting	40 (19)	4 (2)	57 (29)	5 (3)
Infections				
Infections[c]	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection[d]	31 (15)	3 (1)	24 (12)	3 (2)
Pharyngitis	25 (12)	0 (0)	3 (2)	0 (0)
Rhinitis	20 (10)	0 (0)	4 (2)	0 (0)
Musculoskeletal and connective tissue disorders				
Back Pain	41 (20)	6 (3)	28 (14)	7 (4)
Arthralgia	37 (18)	2 (1)	29 (15)	2 (1)
Myalgia	16 (8)	1 (1)	29 (15)	2 (1)

Table 1 –Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial.				
Adverse Reaction	**TORISEL 25 mg n=208**		**IFN-α n=200**	
	All Grades* n (%)	**Grades 3&4* n (%)**	**All Grades* n (%)**	**Grades 3&4* n (%)**
Any	208 (100)	139 (67)	199 (100)	155 (78)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	57 (27)	17 (8)	43 (22)	10 (5)
Cough	54 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
Skin and subcutaneous tissue disorders				
Rash[e]	97 (47)	10 (5)	14 (7)	0(0)
Pruritus	40 (19)	1 (1)	16 (8)	0 (0)
Nail Disorder	28 (14)	0 (0)	1 (1)	0 (0)
Dry Skin	22 (11)	1 (1)	14 (7)	0 (0)
Acne	21 (10)	0 (0)	2 (1)	0 (0)
Nervous system disorders				
Dysgeusia[f]	41 (20)	0 (0)	17 (9)	0 (0)
Insomnia	24 (12)	1 (1)	30 (15)	0 (0)
Depression	9 (4)	0 (0)	27 (14)	4 (2)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
[a] Includes edema, facial edema, and peripheral edema
[b] Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis
[c] Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster
[d] Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection,
[e] Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash
[f] Includes taste loss and taste perversion

The following selected adverse reactions were reported less frequently (<10%).

Gastrointestinal Disorders – Fatal bowel perforation occurred in 1 patient (1%).

Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).

Immune System - Allergic/Hypersensitivity reactions occurred in 18 patients (9%).

Infections - Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).

General Disorders and Administration Site Conditions - Impaired wound healing occurred in 3 patients (1%).

Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.

Vascular - Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Renal – Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.

Intracerebral hemorrhage – Patients with CNS tumors (primary or metastatic) and/or receiving anticoagulant therapy may be at increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

Table 2 – Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial**

Laboratory Abnormality	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Hemoglobin Decreased	195 (94)	41 (20)	180 (90)	43 (22)
Lymphocytes Decreased	110 (53)	33 (16)	106 (53)	48 (24)
Neutrophils Decreased	39 (19)	10 (5)	58 (29)	19 (10)
Platelets Decreased	84 (40)	3 (1)	51 (26)	0 (0)
Leukocytes Decreased	67 (32)	1 (1)	93 (47)	11 (6)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Creatinine Increased	119 (57)	7 (3)	97 (49)	2 (1)
Glucose Increased	186 (89)	33 (16)	128 (64)	6 (3)
Phosphorus Decreased	102 (49)	38 (18)	61 (31)	17 (9)
Total Bilirubin Increased	16 (8)	2 (1)	25 (13)	4 (2)
Total Cholesterol Increased	181 (87)	5 (2)	95 (48)	2 (1)
Triglycerides Increased	173 (83)	92 (44)	144 (72)	69 (35)
Potassium Decreased	43 (21)	0 (0)	15 (8)	0 (0)

*NCI CTC version 3.0

**Grade 1 toxicities may be under-reported for lymphocytes and neutrophils

The following laboratory abnormalities are considered to be adverse drug reactions for TORISEL: anemia, AST increased, hypercholesterolemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, hypokalemia, hypophosphatemia, leukopenia, lymphopenia, neutropenia and thrombocytopenia.

The following summary of clinical pharmacology is also excerpted from the proposed package insert.

Absorption

Following administration of a single 25 mg dose of TORISEL in patients with cancer, mean temsirolimus C_{max} in whole blood was 585 ng/mL (coefficient of variation, CV =14%), and mean AUC in blood was 1627 ng·h/mL (CV=26%). Typically C_{max} occurred at the end of infusion. Over the dose range of 1 mg to 25 mg, temsirolimus exposure increased in a less than dose proportional manner while sirolimus exposure increased proportionally with dose. Following a single 25 mg intravenous dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus.

Distribution

Following a single 25 mg intravenous dose, mean steady-state volume of distribution of temsirolimus in whole blood of patients with cancer was 172 liters. Both temsirolimus and sirolimus are extensively partitioned into formed blood elements.

Metabolism

Cytochrome P450 3A4 is the major isozyme responsible for the formation of five temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes temsirolimus was an inhibitor of CYP2D6 and 3A4. However, there was no effect observed *in vivo* when temsirolimus was administered with desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

Elimination

Elimination is primarily via the feces. After a single IV dose of [^{14}C]-temsirolimus approximately 82% of total radioactivity was eliminated within 14 days, with 4.6% and 78% of the administered radioactivity recovered in the urine and feces, respectively. Following a single 25 mg dose of TORISEL in patients with cancer, temsirolimus mean (CV) systemic clearance was 16.2 (22%) L/h. Temsirolimus exhibits a bi-exponential decline in whole blood concentrations and the mean half-lives of temsirolimus and sirolimus were 17.3 hr and 54.6 hr, respectively.

Effects of Age and Gender

In population pharmacokinetic-based data analyses, no relationship was apparent between drug exposure and patient age or gender.

Clinical Review

The Clinical Review by Virginia Kwitkowski, CRNP (efficacy) and Tatiana Prowell, M.D. (safety) made the following recommendation on regulatory action.

> The clinical reviewers recommend the regular approval of this New Drug Application for temsirolimus for the treatment of advanced renal cell carcinoma (RCC). This recommendation is based upon demonstration of a clinically meaningful and statistically robust improvement in overall and progression-free survival in a randomized, active-controlled, three-arm trial of poor-prognosis patients receiving temsirolimus as first-line treatment of advanced RCC compared to those receiving interferon-a. This was an adequate and well-controlled trial, providing substantial evidence of safety and effectiveness in advanced RCC.
>
> According to the Code of Federal Regulations, section 314.126, addressing adequate and well-controlled trials, the approval of a new drug is contingent upon the demonstration of efficacy and safety by an adequate and well-controlled investigation.
>
> The data support that temsirolimus has an acceptable risk/benefit ratio as recommended in the labeling. Among patients receiving temsirolimus alone, the most common non-laboratory-related treatment emergent adverse events (TEAEs) with an incidence of = 30% are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence =30%) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, hypocalcemia, elevated AST, and neutropenia. The most common grade 3/4 adverse reactions (incidence = 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence = 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia. There is an increased incidence of interstitial lung disease in patients receiving temsirolimus, including rare fatal cases. In some cases, this adverse reaction has recurred with re-treatment. Other rare, serious adverse reactions associated with temsirolimus include bowel perforation (likely due to severe mucositis) and acute renal failure.
>
> Data submitted with this application provide adequate directions for use. The recommended safe and effective dose of temsirolimus has been shown to be 25 mg intravenously weekly. There are known drug interactions with temsirolimus and CYP3A4 inhibitors and inducers. Patients on CYP3A4 inhibitors or inducers

should have alternative therapy. If alternative therapy is not feasible, then temsirolimus dose modifications are recommended as follows:

- Patients who take concomitant medications that are strong CYP3A4 inhibitors should receive a weekly intravenous dose of temsirolimus 12.5 mg.
- Patients who take concomitant medications that are strong CYP3A4 inducers should receive a weekly intravenous dose of up to 50 mg.

A study to assess the potential of QT prolongation is ongoing.

Clinical Team Leader Review

The Clinical Team Leader Review by Amna Ibrahim, M.D. concluded the following:

> Torisel demonstrated a 3.5 month improvement in the median survival and risk reduction of death by 27% in patients with advanced renal cell carcinoma even though patients with a poor prognosis were enrolled in this study. This improvement was demonstrated in comparison to an active control, IFN, which was the community standard of care at the time when the phase 3 study was being designed. No drug has previously been approved for this disease based on an improvement in overall survival. There was also an improvement in PFS and surprisingly only a trend towards an improvement in ORR. Almost all patients experienced some toxicity. Laboratory abnormalities constituted a major proportion of adverse reactions. A few cases of serious and sometimes fatal adverse reactions such as interstitial lung disease, bowel perforation or renal failure occurred in the phase 3 study.
>
> Torisel should be approved based on an improvement in overall survival and an acceptable safety profile in a well-designed, well-conducted randomized study.

Clinical Inspection Summary

The Clinical Inspection Summary was completed on March 12, 2007. The summary stated that "In summary the data provided from the three clinical sites inspected may be used in support of an approval of the submitted NDA."

Statistical Review and Evaluation

The Statistical Review and Evaluation by Shan Sun-Mitchell, Ph.D. made the following conclusions and recommendations.

> This NDA includes a final study report of a single, randomized, comparator-controlled, three-arm registration phase 3 trial, 3066K1-304-WW, in first line-patients with renal cell carcinoma (RCC); the primary endpoint of the study was Overall Survival (OS). Results of the three-arm study demonstrated a median OS

of 10.9 months with temsiroliums 25 mg versus 7.3 months with interferon alpha (IFN). Hazard ratios were 0.73 (95% CI, 0.58-0.92) comparing the temsirolimus 25 mg and IFN arms and 0.96 (95% CI, 0.76-1.20) comparing the combination (temsirolimus 15 mg with IFN) and IFN arms, representing 27% and 4% reduction in risk of death, respectively. The confidence interval for the comparison of temsirolimus 25 mg and IFN did not include 1 (95% CI, 0.58-0.92), and the difference in survival curves between the temsirolimus 25 mg and IFN arms was significant (log-rank p-value=0.0078). The interim analysis of OS crossed the predefined O'Brien-Fleming boundary for superior efficacy of 0.0159 for the comparison of the temsirolimus and IFN arms at 446 events. Overall, the data and results of this NDA submission support the claim of efficacy of temsirolimus in the treatment of advanced renal cell carcinoma.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D. provided the following Executive Summary.

Temsirolimus is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). The current submission is the original NDA for temsirolimus for the treatment of advanced renal cell carcinoma.

To support the approval in advanced renal cell carcinoma, the sponsor conducted one phase 2 and one phase 3 study. Patients in the phase 2 study were randomized to receive 25 mg, 75 mg or 250 mg of temsirolimus IV once weekly. Objective response rate was the primary endpoint and ranged from 5 to 8%. These results indicate that higher doses do not provide further efficacy benefits and therefore the 25 mg/weekly dose was chosen for evaluation in the phase 3 trial.

In the phase 3 study patients were randomly assigned to receive temsirolimus alone, temsirolimus plus interferon, or interferon alone. Preliminary results indicated that the median overall survival rate in the temsirolimus alone arm (25 mg IV once weekly) was 10.9 months. The combination arm and the interferon alone arm had median overall survival rates of 8.4 and 7.3 months respectively.

Based on the results from the drug-drug interaction studies with rifampin and ketoconazole, labeling changes were made to reflect dose adjustments for concomitant administration of CYP3A4 inhibitors and inducers in the Dosage and Administration section. Our recommendations included a dose decrease of 50% for co-administration with potent inhibitors such as ketoconazole. The sponsor proposed a dose increase of 50% when concomitantly administered with potent CYP3A4 inducers, the agency agrees, so this statement was further clarified in the Dosage and Administration section.

The sponsor has two studies currently ongoing, a hepatic study and a thorough QT study. The completion of both studies are to be phase 4 commitments.

The review concluded that "this NDA is considered acceptable from a clinical pharmacology perspective" and recommended the following phase 4 commitments.

> 1. Submit the completed report for the thorough QT prolongation evaluation and datasets for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2- period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects"
>
> 2. Submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US)).

Pharmacology/Toxicology Review and Evaluation

The Executive Summary of the Pharmacology/Toxicology Review and Evaluation provides the major highlights for the nonclinical assessment of temsirolimus. The spectrum of nonclinical studies provided in support of the approval of temsirolimus are consistent with recommendations provided by the Division for products of this class. The Summary notes that there are no nonclinical issues that preclude approval of temsirolimus for the requested indication. However, two particular findings are of note. First, temsirolimus was not genotoxic in the standard battery of genotoxicity tests. While carcinogenicity studies were not conducted for temosirolimus, the major metabolite of temsirolimus was positive in carcinogenicity studies. Second, embryo-fetal toxicities and effects on fertility were noted in reproductive toxicology studies. An addendum to the review discusses the complexities of translating the effects on fertility of temosirolimus administered by oral gavage, to temsirolimus administered by intravenous infusion. The nonclinical findings have been adequately incorporated into the product label.

Chemistry Review

The Chemistry Review by Sarah Pope, Ph.D., Amit Mitra, Ph.D., and David Lewis, Ph.D. made the following recommendation and conclusion on approvability.

> From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable, pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert.

The review also recommended that the following comments and risk management statements regarding CMC should be included in the action letter.

> 1. As stated in the 05-APR-2007 meeting, your proposed Chemistry, Manufacturing and Controls (CMC) Regulatory Agreement, submitted as part of the CMC Pilot program, was not reviewed and is not part of this approval action. Existing regulations and guidances should be followed, as appropriate, for all post-approval CMC changes. We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

2. We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified during this process.

We remind you of our agreements that were made in the 05-APR-2007 teleconference and in your submission dated 12-APR-2007. These agreements are listed below:
1. You have agreed to investigate the use of a flag label, or a suitable alternative, in order to incorporate additional information in the container labels for both the diluent and active vials.
2. You have agreed to submit the developed strategy for the above agreement in a Prior Approval supplement.
3. You have agreed to further discussions with the Agency regarding packaging technology options available, to ensure the physical connection of the two co-packaged vials.

The memorandum from Sarah Pope, Ph.D., on May 29, 2007 noted that final acceptable container/carton labeling was submitted on May 25, 2007 and that agreement on the CMC aspects of the package insert was reached in a teleconference on May 29, 2007. The conclusion of the memo was that from a CMC standpoint, the application is recommended for approval.

The ONDQA Division Director's CMC Memorandum by Chi-Wan Chen, Ph.D., dated March 25, 2007, also recommended approval from the CMC standpoint.

Microbiology Review

The Product Quality Microbiology Review by Stephen Langille, Ph.D. recommended approval on the basis of product quality microbiology.

DDMAC Comments on Draft Labeling

DDMAC Comments on Draft Labeling by Joseph Grillo are dated February 28, 2007 and were considered during the internal labeling meetings.

DMETS Comments on Draft Labeling

The DMETS review of the proposed container labels, carton and insert labeling by Carol Holquist, R.Ph. was completed by Carol Holquist, R.Ph. on February 16, 2007. The review made a number of important recommendations which were incorporated into labeling.

OSE Temsirolimus Risk Management Team Consultation

The OSE consultation on the proposed Risk Management Plan dated April 5, 2007 made the following conclusions and recommendations.

Based on the information provided at this time and considering the patient population, severity of RCC, mortality of RCC, limited treatment options[5] (Proleukin,[6] Nexavar,[7] interferon alfa), comparable level of risks associated with other treatment options and with other chemotherapeutic agents in general, along with the limited scope of the prescribing population; it appears that the Sponsor's proposal is a reasonable approach to manage the risks at this time. The use of education (e.g., drug interaction reference guide) may be beneficial and can occur outside of a risk minimization action plan. At present, the current initiatives proposed by Wyeth do not constitute a formal risk minimization action plan.

OSE had recommendations on the draft labeling, medication error reporting, and the drug interaction reference guide which were considered during the internal labeling meetings.

Conclusion

This is the first drug in advanced renal cell cancer which has demonstrated a statistically and clinically significant improvement in median survival from 7.3 months with IFN-α to 10.9 months with temsirolimus. In addition, there was also an improvement in PFS from 3.1 to 5.5 months. Although the objective response rate was higher with temsirolimus the difference was not statistically significant. As noted above, this improvement in overall survival was accompanied by significant but generally manageable toxicity. I concur with the recommendations for approval of this NDA.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
5/30/2007 12:44:49 PM
MEDICAL OFFICER

CLINICAL TEAM LEADER'S REVIEW OF AN NDA
DIVISION OF DRUGS ONCOLOGY PRODUCTS
OFFICE OF ONCOLOGY

NDA	22,088
Drug Name	Temsirolimus, previously known as CCI-779
Trade Name	Torisel
Submission Code	00
Priority Designation:	Priority review
Applicant	Wyeth Pharmaceuticals
Indication	Treatment of advanced renal cell carcinoma
Letter Date	October 5th, 2006
Date of Review:	May 29th, 2007

Recommendation:
This NDA should be approved for the following indication:

"Treatment of advanced renal cell carcinoma"

In a well-designed, well-conducted prospectively randomized study, Torisel demonstrated a robust improvement in overall survival when compared with an active control, interferon-α (IFN), a drug that was the standard of care at the time when the trial was designed. The risk/benefit ratio is acceptable.

Introduction:
Torisel is kinase inhibitor and its purported mechanism of action is inhibition of mTOR and prevention of progression from G1 to S phase of the cell cycle. Its major metabolite, sirolimus is approved as Rapamune for prophylaxis of organ rejection in patients 13 years or older receiving renal transplant.

Torisel is the third drug to be approved by the FDA in 18 months for advanced renal cell cancer, and the first to be approved for based on an improvement in overall survival for this indication. Sorafenib (Nexavar) was approved in December 2005 based on a 2.8 month improvement in median progression-free survival (PFS) when compared with placebo. In January 2006, sunitinib (Sutent) received an accelerated approval based on durable responses. A randomized study comparing Sutent to IFN in treatment naïve patients with advanced renal cell cancer was the basis for its conversion to a regular approval in February 2007. An improvement in approximately 6 months in PFS at a planned interim analysis was observed. Proleukin (IL-2) is also approved, but is considered to be a toxic therapy for renal cancer with a low response rate and no proven benefit in survival. IFN although not approved had been the most widely used treatment of advanced renal cancer prior to availability of the kinase inhibitors. An improvement in survival has been claimed for IFN from results of randomized trials in published literature.

An interim analysis of a single prospectively randomized trial (3066K1-304-WW) provides the basis of efficacy and safety for this NDA and will be discussed in this document. The design of this study underwent a special protocol assessment (SPA) and was acceptable to the Agency.

Review of the Randomized Phase 3 Study

Protocol Number:
3066K1-304-WW

Protocol Title:
A Phase 3, Three-Arm, Randomized, Open-Label Study of Interferon Alfa Alone, CCI-779 Alone, and the Combination of Interferon Alfa and CCI-779 in First-Line Poor-Prognosis Subjects with Advanced Renal Cell Carcinoma

Study Dates:
June 2003-May 2006

Study Sites:
148 sites in 23 countries

Study Design:
A prospectively, randomized three-arm study accrued 626 patients with previously untreated advanced renal cancer were randomized to one of three arms; Single agent IFN, single agent temsirolimus and a combination of IFN and temsirolimus (TEM). Patients in this study had 3 or more of 6 pre-selected prognostic risk factors. These criteria were less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site. These criteria have been described in literature (JCO; Vol 23, No 4 (February 1), 2005: pp. 832-841). Patients were stratified for prior nephrectomy status within three geographic regions.

The primary endpoint was overall survival and secondary endpoints included PFS, overall and response rate (ORR). Secondary objectives also included a primary health outcome measure.

Patients were to be followed for survival during the treatment period by regularly scheduled clinic visits. Patients who discontinued treatment were followed for survival every 2 months by telephone contact. At the request of the IDMC, patients were also contacted by the investigators prior to each interim analysis to verify their survival status. Patients underwent radiographic evaluation (chest CT, abdominal/pelvic CT, brain scan [MRI or CT with contrast], bone scan, and plain films of bone scan abnormalities [x-ray or CT]) at screening, approximately every 8 weeks until disease progression. The original films were also sent to a central imaging service provider for an independent review. Responses were to be assessed according to RECIST criteria. In an amendment which was not part of the SPA agreement, the response criteria were modified such that patients with bone only disease assessed by MRIs could be enrolled in to the study.

Table 1: Study Arms, Regimens and Number of Patients Randomized

	TEM	IFN	IFN + TEM
Randomized	209	207	210
Treated	208	200	208
Dosage	25 mg weekly IV	3 MU 3 times in 1st week then 9 MU 3 times in 2nd week then, 18 MU 3 times weekly	IFN: 3 MU 3 times in 1st week then 6MU 3 times weekly Temsirolimus: 15 mg weekly IV

Review of data from two formal interim analyses by an independent data monitoring committee (IDMC) of unblinded efficacy was planned. Decisions to recommend early termination of the study for efficacy benefit or lack of benefit were to be made based on results from each of the two interim analyses.

In the original protocol, one interim analysis using the O'Brien-Fleming boundary for superior efficacy was planned to guide the decision to declare early success; early futility was to be declared based on conditional power. Protocol amendment 4 was implemented prospectively, which added a second interim analysis. The first interim analysis was to be conducted after 164 deaths had occurred, and the second interim analysis after approximately 430 deaths. When the second interim analysis was added, the critical p-value was adjusted to preserve an overall 5% significance level. For the second interim analysis, if the p-value was less than or equal to 0.0135, then the alternative hypothesis of treatment difference was to be accepted. If the conditional powers for the 2 comparisons (IFN vs. temsirolimus and IFN vs. the temsirolimus/IFN combination) were both less than 10%, consideration was to be given to stopping for early failure. For the final analysis after approximately 504 deaths, the O'Brien-Fleming boundary is 0.0211.

Demography:
The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy. Approximately a third of the patients were from the US. Twenty percent of patients were in follow-up phase and 5% remained on treatment at the time of data-lock date.

There were few major protocol violations. One patient did not have histological or cytological diagnosis of advanced renal cell carcinoma. Four patients had symptomatic brain metastases. Three of the randomized patients had received prior therapy. Six patients had fewer than 3 factors at randomization. Seventeen patients had laboratory abnormalities beyond the protocol specified guidelines.

Table 2: Patient Disposition in ITT Population (applicant table)

	TEM	IFN	IFN + TEM	Total
Patient Disposition (n, %)	(n=209)	(n=207)	(n=210)	(n=626)
Alive	58 (27.8)	45 (21.7)	51 (24.3)	154 (24.6)
On treatment	9 (4.3)	6 (2.9)	15 (7.1)	30 (4.8)
In follow-up	49 (23.4)	39 (18.8)	36 (17.1)	124 (19.8)
Died	147 (70.3)	152 (73.4)	154 (73.3)	453 (72.4)
Lost to follow-up*	4 (1.9)	10 (4.8)	5 (2.4)	19 (3.0)

* Lost to follow up includes 9 patients who withdrew consent (3 in IFN arm, 3 in temsirolimus arm, and 3 in combination arm) and 2 patients in the IFN arm who discontinued for other reasons (SAE before first dose of IFN and disease progression).

Exposure:

The median duration of treatment in the Torisel arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks). In the combination arm, the median duration of IFN was 12 weeks and 15 weeks for Torisel. Patients in the single agent Torisel arm received almost full intensity Torisel, whereas the dose intensity was reduced to 75% in the combination arm.

Efficacy Results:

Table 3: Summary of Efficacy Results of Torisel vs. IFN

Parameter	TEM n = 209	IFN n = 207	P-value[a]	Hazard Ratio (95% CI)[b]
Median OS Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0078*	0.73 (0.58, 0.92)
Median PFS Months (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	0.0001**	0.66 (0.53, 0.81)
ORR % (95% CI)	8.6 (4.8, 12.4)	4.8 (1.9, 7.8)	0.1232**[c]	NA

CI = confidence interval; NA = not applicable

* A comparison is considered statistically significant if the p-value is <0.0159 (O'Brien-Fleming boundary at 446 deaths).

** Not adjusted for multiple comparisons.

[a]. Based on log-rank test stratified by prior nephrectomy and region.

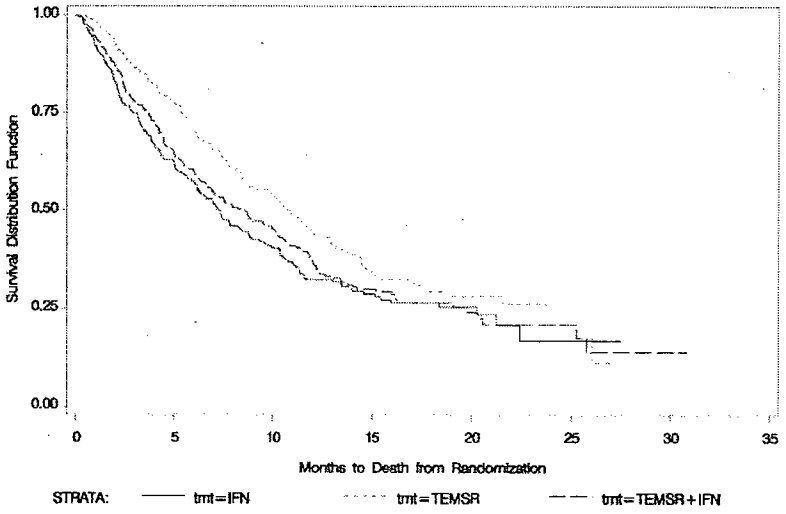
[b]. Based on Cox proportional hazard model stratified by prior nephrectomy and region.

[c]. Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

Overall Survival:

The clinical and statistical review confirmed the improvement in OS. Single agent Torisel arm demonstrated a 3.5 month improvement in median survival when compared to single agent IFN, with a risk reduction of 27% in death. The results for OS in the Torisel combination arm were similar to those in the single agent IFN arm (HR: 0.96 [0.76-1.2]).

Figure 1: Overall Survival in the ITT population (Applicant figure)



As subsequent therapy, patients on the Torisel arm had IFN as a treatment option but the reverse was not true for the patients on the IFN arm because Torisel was not widely available (see table 4). However, subsequent therapy does not appear to skew the results in favor of the patients on the Torisel arm. An exploratory analysis performed by the sponsor. In this analysis, OS was evaluated in patients who did not receive any subsequent therapy after Torisel (TEM: n=129 and IFN: n=153). Hazard ratio was similar to that in the ITT population (HR: 0.73[95% C.I., 0.56-0.98]). At a minimum, Torisel treatment adds to overall survival when given first-line to patients with advanced renal cancer.

Table 4: Frequency of Select Subsequent Therapy (from the Applicant table)

Number of patients who received subsequent therapy	**TEM N=209**	**IFN N=207**	**IFN + TEM N=210**
Interferon	48	15	18
IL2	11	13	5
Bevacizumab	12	10	6
Sorafenib	8	6	5
Sunitinib	2	2	6

Progression-Free Survival (PFS) and Overall Response Rate (ORR):
The median PFS was improved by approximately 2.5 months in the single agent Torisel arm when compared to the single agent IFN arm. The response rate demonstrated only a trend towards improvement in the Torisel arm compared to the control. This was may be due to the reduced exposure in the combination arm to Torisel.

Safety:
A total of 616 patients were treated. Two hundred patients received IFN weekly, 208 received TORISEL 25 mg weekly, and 208 patients received a combination of TORISEL and IFN-α weekly. Treatment with the combination of TORISEL 15 mg and IFN was

associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in overall survival when compared with IFN-α alone.

The most common (≥ 30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥ 30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and neutropenia. The most common grade 3/4 adverse reactions (incidence ≥ 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence ≥ 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.

Because the major metabolite of Torisel is sirolimus, a known immunosuppressant, propensity to infections was a concern. Approximately 14% of patients were reported to have had an infection on the Torisel arm compared to 4.5% on the IFN arm. There is an increased incidence of interstitial lung disease in patients receiving temsirolimus, including rare fatal cases. In some cases, this adverse reaction has recurred with re-treatment. Other rare, serious adverse reactions associated with temsirolimus include bowel perforation likely due to severe mucositis and acute renal failure. A few of the patients with renal failure had a rapidly progressive course ending in death.

Drug interactions:
Strong inducers and inhibitors of CYP3A4 may affect concentrations of the primary metabolite of Torisel. If alternatives cannot be used, dose modifications of Torisel should be considered.

Major Amendment:
Response criteria in the original protocol were based on RECIST. This was later amended to a modified version of RECIST where bone lesions were considered measurable if evaluated by MRI and patients with bone only lesions could be enrolled. However, the independent, blinded investigator included bone lesions measured by CT scans and in patients who had measurable soft tissue lesions in the analysis. From the information provided in the datasets, it was not possible for the FDA review team to reassess PFS and ORR as prespecified in the protocol. At the FDA's request, the applicant reassessed the tumor responses as specified in amendment 1 of the protocol. Due to this and due to late submission of missing datasets for tumor measurements and laboratory abnormalities, the PDUFA date was extended by 3 months to July 7th, 2007. Action on this NDA is expected in early June 2007.

Overall, radiographs for 7 patients were reread because the patients originally had bone only target lesions and/or more than 5 target lesions selected within a single organ. The results on the Torisel or IFN arm did not change after this re-analysis. The median PFS for the combination arm changed from 4.9 months to 4.7 months.

Phase 4 commitments:
There will be two phase 4 commitments; one is a study to evaluate the effect of Torisel on QT prolongation, and the other is a hepatic impairment study. Both these studies are ongoing.

Conclusion:
Torisel demonstrated a 3.5 month improvement in the median survival and risk reduction of death by 27% in patients with advanced renal cell carcinoma even though patients with a poor prognosis were enrolled in this study. This improvement was demonstrated in comparison to an active control, IFN, which was the community standard of care at the time when the phase 3 study was being designed. No drug has previously been approved for this disease based on an improvement in overall survival. There was also an improvement in PFS and surprisingly only a trend towards an improvement in ORR. Almost all patients experienced some toxicity. Laboratory abnormalities constituted a major proportion of adverse reactions. A few cases of serious and sometimes fatal adverse reactions such as interstitial lung disease, bowel perforation or renal failure occurred in the phase 3 study.

Torisel should be approved based on an improvement in overall survival and an acceptable safety profile in a well-designed, well-conducted randomized study.

Amna Ibrahim M.D
Acting Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim
5/29/2007 12:13:27 PM
MEDICAL OFFICER

CLINICAL SAFETY REVIEW ADDENDUM

NDA	22,088
Drug Name	Temsirolimus, previously known as CCI-779
Trade Name	Torisel
Submission Code	00
Priority Designation:	Priority review
Applicant	Wyeth Pharmaceuticals
Indication	Treatment of advanced renal cell carcinoma
Letter Date	October 5th, 2006
Date of Review:	May 29th, 2007
Date of Addendum	May 30th, 2007

There was a discrepancy between Wyeth and FDA frequencies of some laboratory abnormalities (Table 2 in label). This document addresses these discrepancies and the final results of the re-analyses on the next page.

The abnormalities in question were the incidence of decrease in serum phosphorus, potassium lymphocytes and neutrophils, and increase in total bilirubin, total cholesterol, and triglycerides.

These were reanalyzed by Wyeth and FDA. The correct incidence is as presented in the table below.

Grade 1 toxicity and consequently all grade toxicity for lymphopenia and neutropenia may be underreported. This was because the datasets captured neutrophils and lymphocytes as percentages of total WBC, whereas NCI CTC grade 1 toxicity for these abnormalities depends on an absolute number for lower limit of normal. For example, a certain percentage of neutrophils may be low when compared to the WBC count, but the absolute number may be within normal limits. Underreporting of these grade 1 laboratory abnormalities will not adversely affect the patients who will be treated with Torisel.

Table 2 in the label will appear as on the next page.

Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

Laboratory Abnormality	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Hemoglobin Decreased	195 (94)	41 (20)	180 (90)	43 (22)
Lymphocytes Decreased**	110 (53)	33 (16)	106 (53)	48 (24)
Neutrophils Decreased**	39 (19)	10 (5)	58 (29)	19 (10)
Platelets Decreased	84 (40)	3 (1)	51 (26)	0 (0)
Leukocytes Decreased	67 (32)	1 (1)	93 (47)	11 (6)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Creatinine Increased	119 (57)	7 (3)	97 (49)	2 (1)
Glucose Increased	186 (89)	33 (16)	128 (64)	6 (3)
Phosphorus Decreased	102 (49)	38 (18)	61 (31)	17 (9)
Total Bilirubin Increased	16 (8)	2 (1)	25 (13)	4 (2)
Total Cholesterol Increased	181 (87)	5 (2)	95 (48)	2 (1)
Triglycerides Increased	173 (83)	92 (44)	144 (72)	69 (35)
Potassium Decreased	43 (21)	[redacted]	15 (8)	0 (0)

*NCI CTC version 3.0

**Grade 1 may be under-reported for lymphocytes and neutrophils

Amna Ibrahim MD
Acting Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim
5/30/2007 01:43:04 PM
MEDICAL OFFICER
Clinical safety review addendum for laboratory abnormalities

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-088
Submission Code	00
Letter Date	10/05/06
Stamp Date	10/05/06
PDUFA Goal Date	07/05/07
Reviewer Names	Efficacy: Virginia Kwitkowski, CRNP Safety: Tatiana Prowell, MD
Review Completion Date	05/25/07
Established Name	temsirolimus
Proposed Trade Name	Torisel
Therapeutic Class	Kinase Inhibitor
Applicant	Wyeth
Priority Designation	Priority
Formulation	Intravenous infusion
Dosing Regimen	25mg weekly
Indication	Treatment of advanced renal cell carcinoma
Intended Population	Patients with advanced renal cell carcinoma

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Wyeth Pharmaceuticals Inc. submitted NDA 22088 for the following indication

"TORISEL is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma"

The clinical reviewers recommend the regular approval of this New Drug Application for temsirolimus for the treatment of advanced *renal cell carcinoma* (RCC). This recommendation is based upon demonstration of a clinically meaningful and statistically robust improvement in overall and progression-free survival in a randomized, active-controlled, three-arm trial of poor-prognosis patients receiving temsirolimus as first-line treatment of advanced RCC compared to those receiving interferon-α. This was an adequate and well-controlled trial, providing substantial evidence of safety and effectiveness in advanced RCC.

According to the Code of Federal Regulations, section 314.126, addressing adequate and well-controlled trials, the approval of a new drug is contingent upon the demonstration of efficacy and safety by an adequate and well-controlled investigation.

The data support that temsirolimus has an acceptable risk/benefit ratio as recommended in the labeling. Among patients receiving temsirolimus alone, the most common non-laboratory-related treatment emergent adverse events (TEAEs) with an incidence of ≥ 30% are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, hypocalcemia, elevated AST, and neutropenia. The most common grade 3/4 adverse reactions (incidence ≥ 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence ≥ 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.
There is an increased incidence of interstitial lung disease in patients receiving temsirolimus, including rare fatal cases. In some cases, this adverse reaction has recurred with re-treatment. Other rare, serious adverse reactions associated with temsirolimus include bowel perforation (likely due to severe mucositis) and acute renal failure.

Data submitted with this application provide adequate directions for use. The recommended safe and effective dose of temsirolimus has been shown to be 25 mg intravenously weekly. There are known drug interactions with temsirolimus and CYP3A4 inhibitors and inducers. Patients on CYP3A4 inhibitors or inducers should have alternative therapy. If alternative therapy is not feasible, then temsirolimus dose modifications are recommended as follows:

- Patients who take concomitant medications that are strong CYP3A4 inhibitors should receive a weekly intravenous dose of temsirolimus 12.5 mg.
- Patients who take concomitant medications that are strong CYP3A4 inducers should receive a weekly intravenous dose of up to 50 mg.

A study to assess the potential of QT prolongation is ongoing.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Unusual toxicities that are seen with temsirolimus include interstitial lung disease, bowel perforation, renal failure, dyspnea, hyperglycemia, infections, and drug-drug interactions, and will be described in the labeling. The Sponsor will conduct post-marketing pharmacovigilance activities to evaluate safety signals associated with temsirolimus.

1.2.2 Required Phase 4 Commitments

1.2.2.1 Submit the completed report for the thorough QT prolongation evaluation and datasets for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2- period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects"

Protocol Submission: March 2006
Study Start: March 2006
Final Report Submission: September 2007

1.2.2.2 Submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US))

Protocol Submission: November 2005
Study Start: January 2006
Final Report Submission: September 2008

1.2.3 Other Phase 4 Requests

1.2.3.1 Pediatric Written Request
The Applicant should submit study reports and raw data for pediatric PK and clinical studies in order to fulfill the requirements for a pediatric exclusivity extension under section 505A of the Best Pharmaceuticals for Children Act. [redacted]

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Temsirolimus is a first-in-class specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. It exerts its effect on cell proliferation by inhibiting m-TOR-dependent protein translation induced by growth factor stimulation of cells. Temsirolimus has shown activity against a wide variety of human tumor types *in vitro* and *in vivo* in nude mouse xenografts. The compound prevents progression from G1 to S phase of the cell cycle through inhibition of mTOR, which is a novel mechanism of action for an anti-cancer drug. Temsirolimus is a pro-drug of sirolimus which is marketed as Rapamune for the prophylaxis of organ rejection in renal transplant patients 13 years or older. Temsirolimus is administered as an IV infusion dosed at 25 mg weekly. It is indicated for the treatment of adults with advanced renal cell carcinoma.

The Applicant submitted information on one phase 3, pivotal efficacy trial and one phase 2 dose-finding trial. The phase 3 trial enrolled 626 patients, with 416 patients receiving at least one dose of temsirolimus. In the phase 3 trial, 305 patients randomized to receive temsirolimus, received at least 8 weeks of exposure to the drug. Crossover to a non-randomized treatment arm was not permitted. In the temsirolimus arm the median exposure to temsirolimus was 17 weeks (range 1-126 weeks).

1.3.2 Efficacy Results

Efficacy Study
A single phase 3, multi-center, three-arm, randomized, open-label study was conducted in 626 previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies) carcinoma. The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients. The trial contained three randomized treatment groups: 1) temsirolimus 25 mg (intravenous) weekly; 2) interferon-α (subcutaneous) three times weekly; and 3) temsirolimus 15 mg (intravenous) weekly plus interferon-α. The patients received treatment until evidence of disease progression or intolerable toxicity. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site).

Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n=207), TORISEL alone (25 mg weekly; n=209), or the combination arm (n=210).[i]

The second interim analysis of the phase 3 randomized, active-controlled trial was submitted as evidence of the efficacy of temsirolimus for the indication of advanced renal cell cancer. The study is ongoing at the time of this review. The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

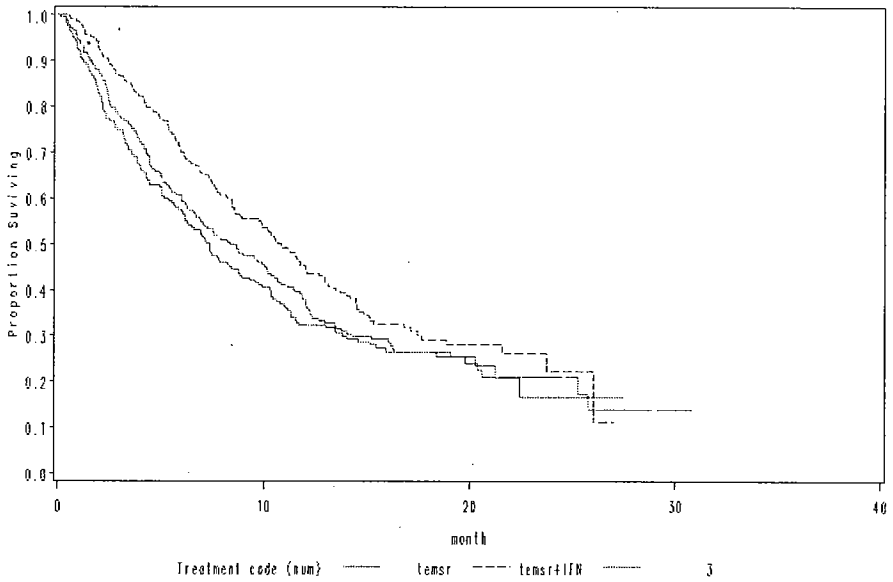
There was a statistically significant improvement in overall survival (OS), defined as time from randomization to death in the TORISEL 25 mg arm compared to the IFN-α. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in overall survival when compared with IFN-α alone and is not shown in table 1.1. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of progression-free survival (PFS) and objective response rate (ORR), were based on blinded independent radiologic assessment of tumor response using RECIST-based criteria. An improvement in PFS in the TORISEL 25 mg arm was seen. The p-value was 0.0001 (not adjusted for multiple comparisons).

Table 1.1 Summary of Efficacy Results of TORISEL vs. IFN-α

Parameter	TORISEL n = 209	IFN-α n = 207	P-value[a]	Hazard Ratio (95% CI)[b]
Median Overall Survival Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0078*	0.73 (0.58, 0.92)
Median Progression-Free Survival Months (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	0.0001**	0.66 (0.53, 0.81)
Overall Response Rate % (95% CI)	8.6 (4.8, 12.4)	4.8 (1.9, 7.8)	0.1232[c**]	NA

CI = confidence interval; NA = not applicable
* A comparison is considered statistically significant if the p-value is <0.0159 (O'Brien-Fleming boundary at 446 deaths).
** unadjusted for multiple comparisons.
a. Based on log-rank test stratified by prior nephrectomy and region.
b. Based on Cox proportional hazard model stratified by prior nephrectomy and region.
c. Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

Figure 1.1 Kaplan-Meier Curve Representing Overall Survival Between Treatment Arms



The conduct of the study appeared to be adequate, and no major issues were raised during DSI audits of the three top enrolling sites. The statistical analysis was adequate and pre-specified for

all important endpoints. Due to essential safety data and data needed for evaluation of RR and PFS was submitted late in the review, the PDUFA date was extended. The RECIST criteria for response assessment were not adhered to as planned in the original protocol. RECIST criteria state "lesions considered to be truly non-measurable include the following: bone lesions...," and the protocol stated that RECIST criteria would be utilized (with the exception of the enrollment of patients with bone-only disease). Amendment 1 of the protocol did allow for enrollment of patients with bone-only metastases and specified that their tumors would be measured by MRI. This amendment was not an amendment to the Special Protocol Assessment and was not agreed to by the FDA. It was discovered that bone lesions were not measured by MRI in all bone-only patients (CT and other forms of imaging were used to measure these lesions). In addition, it was discovered that patients who met the RECIST criteria for measurable soft-tissue disease in fact had bone metastases measured and recorded as target lesions. The review team requested that the Applicant re-analyze the tumor datasets and remove all target bone lesions. The datasets were not entirely clear with regard to which lesions were of bone versus soft tissue, and were reanalyzed by the independent reviewers. The results of the re-analyses were found to be acceptable to the review Division.

Efficacy Conclusions:

- The results of the randomized, controlled trial provide substantial evidence of efficacy of temsirolimus as a single agent in advanced renal cell carcinoma.

- A statistically significant overall survival advantage was demonstrated in patients who were randomized to the temsirolimus group compared to those who were randomized to the interferon alfa group.

- An improvement in median progression free survival (unadjusted for multiple comparisons) was demonstrated in patients who were randomized to temsirolimus vs. interferon-alfa.

- Overall response rate was higher in the patients treated with temsirolimus alone vs. interferon alfa, but this difference did not reach statistical significance and was unadjusted for multiple comparisons.

- The Q-TWiST analysis could not be supportive of clinical benefit due to multiple limitations in the design, plan, tool, and inequality in missing data.

Temsirolimus adds to the current armamentarium for the treatment of advanced renal cell carcinoma because it improves overall survival in a treatment-naïve, advanced, poor-prognosis patient population. This is the first drug to be approved for an improvement in overall survival. No comparative studies have yet been performed with the oral kinase inhibitors recently approved for advanced renal cell carcinoma (Sutent and Nexavar).

1.3.3 Safety

Safety Studies

A total of 1,080 individuals enrolled in 20 clinical studies who have received IV temsirolimus form the basis of the original safety database for this NDA. This includes 416 subjects in the randomized phase III trial in advanced RCC, 179 subjects in phase I and phase II studies of advanced RCC, 178 subjects in three studies of other cancers (breast, prostate, and mantle cell lymphoma), 215 subjects in seven phase I studies in advanced solid tumors, and 92 healthy subjects in five phase I studies. The results from the phase 3 trial in first-line treatment of advanced RCC were used as the foundation of the safety analysis with use of the remainder of the safety database for assessment of serious or rare AEs. Information on adverse events (AEs) was available until the data lock date of 05/30/2006 in the sponsor's original NDA submission. The Safety Update submitted 01/04/2007 provided data through the data lock date of 10/02/2006 and included data on a total of 1,163 subjects.

A phase 2, randomized, double-blind, multi-center trial of 111 patients with advanced renal cell carcinoma was also submitted in support of this application. In this trial, patients were randomized in a 1:1:1 ratio to receive 25 mg, 75 mg, or 250 mg of temsirolimus weekly until evidence of disease progression. This trial justifies the selected monotherapy dose of 25 mg for the phase 3 trial and for safety.

Please see Section 4.2 for a tabular listing of all trials using temsirolimus in the clinical program.

In the randomized phase 3 trial of temsirolimus in advanced renal cell carcinoma (3066K1-304-WW), a clinical examination and measurement of coagulation parameters were performed at least every 4 weeks during treatment. A fasting chemistry panel was performed every 2 weeks, and a complete blood count (CBC) was performed weekly. Electrocardiograms (ECGs) were performed at the screening visit and at the time of study withdrawal for all patients, and at two additional visits (first treatment and at three months) for a subset of patients enrolled in US and Canadian sites. A quality of life assessment tool (Euroqol EQ-5D) was administered weekly during treatment, and patients had weekly clinic visits at which they were encouraged to report adverse events. Adverse events were recorded in the case report forms (CRF) with NCI toxicity grade, dates of onset and resolution, attribution of relationship to test article, outcome, and specific laboratory values where relevant.

In the Phase 3 trial, the median duration of therapy for patients on the temsirolimus was 17 weeks (range: 1-126 weeks) compared with 8 weeks for the IFN-α arm (range: 1-124 weeks). Virtually all patients in every treatment arm of the phase 3 study experienced at least one treatment-emergent adverse event (TEAE), and almost half of the patients had at least one serious adverse event (SAE). Single-agent temsirolimus was associated with a lower overall incidence of grade 3 and 4 TEAEs and SAEs than interferon or the combination. The incidence of TEAEs leading to treatment discontinuation and dose reduction was also lowest in the temsirolimus alone arm, although the temsirolimus alone arm had a higher incidence of TEAEs leading to dose delays.

The most common adverse reactions (incidence ≥ 30%) were rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) were anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, hypocalcemia, elevated AST, and leukopenia.

The most common grade 3/4 adverse reactions (incidence ≥ 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence ≥ 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.

Rare serious adverse reactions associated with temsirolimus included interstitial lung disease, bowel perforation, and acute renal failure.

No limitations were identified during the review of this application in the safety findings.

During labeling discussions, on 5/23/07, Wyeth notified FDA of safety data from a recently terminated Phase 1/2 trial evaluating the combination of Torisel and Sutent in the treatment of advanced RCC. This trial enrolled three patients to the first cohort (Torisel 15 mg IV weekly plus Sutent 25 mg by mouth daily days 1-28 followed by a 2 week rest). Of these three patients in cohort 1, two developed dose-limiting toxicities (DLTs). The first DLT was Grade 3/4 erythematous maculopapular rash and the second DLT was cellulitis and gout requiring hospitalization. This information indicates that the combination of Torisel and Sutent at the tested doses was not safe or tolerable. At the time of this review, discussions are ongoing as to whether this information will be in the label document for this submission.

1.3.4 Dosing Regimen and Administration

Temsirolimus is dosed at 25mg infused intravenously over a 30-60 minute period once per week. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Pre-medication with an anti-histamine (such as diphenhydramine) is recommended. Treatment is recommended in adults only.

Dose reductions may be made by 5 mg weekly for toxicity with no more than 3 dose reductions recommended.

1.3.5 Drug-Drug Interactions

There are drug-drug interactions related to CYP-3A4 metabolism. Dose reduction to 12.5 mg weekly is recommended for patients who must receive concomitant CYP3A4-inhibitors. Dose increases to 50 mg weekly are recommended for patients who must receive concomitant CYP3A4-inducers.

1.3.6 Special Populations

Hepatic Impairment
A study evaluating the use of temsirolimus in a population with hepatic impairment is ongoing. Data from this study was not provided with this application. According to the Applicant, the initial safety and PK data available on 14 patients indicate that thrombocytopenia was dose limiting for patients with mild hepatic impairment, leading to de-escalation and multiple dose delays. Their review of the available PK data has led Wyeth to conclude that that the limited tolerability of temsirolimus in these patients was fully explained by differences in PK disposition.

Renal Impairment
The available data indicate that renal elimination plays a minor role in the clearance of temsirolimus. Study 3066K-133-US obtained mass balance data in which mean urinary excretion following the 25 mg IV temsirolimus dose was approximately 5%. The integrated population PK analysis of temsirolimus and sirolimus informed that PK disposition was not affected by differences in creatinine clearance.

Racial Differences
PK data obtained from study 3066K1-131-JA demonstrated that the intravenous temsirolimus exposures between Japanese and non-Japanese patients are similar. No justification for dose alteration or regimen exists for this patient population.

Pediatrics
A PK assessment is included in an ongoing Phase 1/2 study in pediatric patients with cancer (3066K1-139-US). The data are not yet available.

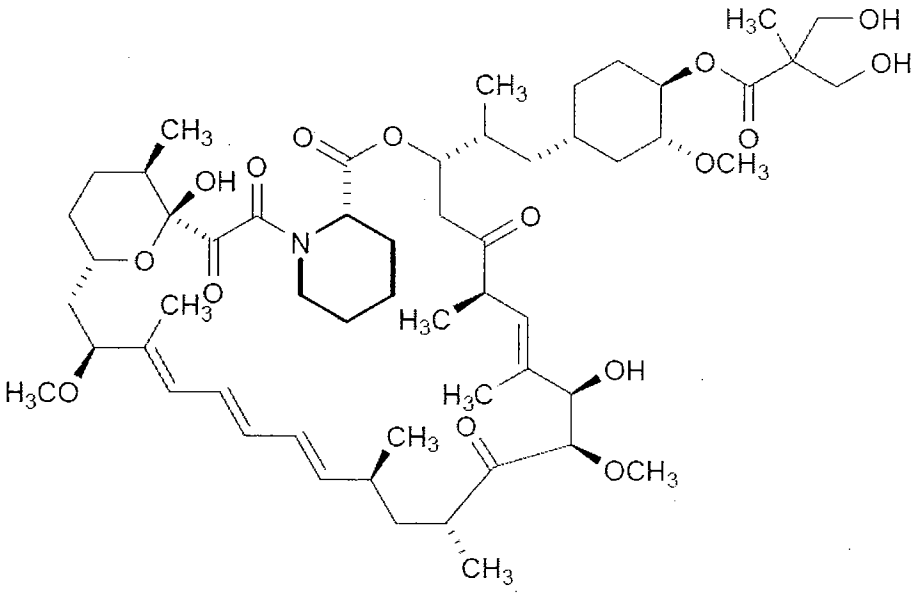
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Temsirolimus is a first-in-class specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. It exerts its effect on cell proliferation by inhibiting mTOR-dependent protein translation induced by growth factor stimulation of cells. Temsirolimus has shown activity against a wide variety of human tumor types *in vitro* and *in vivo* in nude mouse xenografts. The compound prevents progression from G1 to S phase of the cell cycle through inhibition of mTOR, which is a novel mechanism of action for an anticancer drug. Tumors (e.g. prostate, glioma) with deletions in the PTEN tumor suppressive gene show hyperactivity of the Akt-mTOR pathway, providing a strong rationale to investigate the use of temsirolimus in these tumors. The finding that mTOR regulates protein synthesis of HIFs (hypoxia inducible factors that regulate tumor angiogenesis and survival pathways that permit tumor growth in the harsh microenvironment induced by hypoxia) suggests that many solid tumors would be negatively affected by temsirolimus inhibition of mTOR. In particular, since approximately 80% of RCCs have lost the VHL gene, the growth of this tumor type may be particularly sensitive to treatment with temsirolimus. The VHL gene is a negative regulator of HIF-1,2a and its loss in RCC results in increased levels of HIF and subsequent increased transcription of VEGF. Down regulation of HIF by temsirolimus may in part explain its activity in RCC.

Temsirolimus is administered as an IV infusion with 0.9% Sodium Chloride Injection. A two-component dosage form is supplied to permit preparation of the intravenous admixture. Temsirolimus Concentrate for Injection 25 mg/mL is a clear, colorless to light yellow, non-aqueous, ethanolic, sterile solution, essentially free from visual particulates, packaged in [redacted] glass vials with a [redacted] stopper. Temsirolimus Concentrate for Injection contains a mixture of propylene glycol, dehydrated alcohol (39.5% w/v), dl, a-tocopherol (0.075%, [redacted] and a small quantity of anhydrous citric acid (0.0025%, [redacted]. The diluent consists of a mixture of polysorbate 80 (40% w/v), dehydrated alcohol (19.9% w/v) in polyethylene glycol 400, packaged in a [redacted] glass vial using the same [redacted] stoppers as the temsirolimus concentrate. The temsirolimus concentrate is combined with the diluent in a ratio of 1.[redacted] to produce a 10 mg/mL solution of drug for admixture preparation.

Figure 2.1. Molecular Structure of temsirolimus



Established Name: temsirolimus
Proposed Trade Name: Torisel ™
Chemical Class: New molecular entity
Proposed Indication: Advanced Renal Cell Carcinoma
Applicant Proposed Dosing Regimen: Temsirolimus is dosed at 25mg infused intravenously over a 30-60 minute period once per week. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Pre-medication with an anti-histamine (such as diphenhydramine) is recommended. Treatment is recommended in adults only.

2.2 Currently Available Treatment for Indication

Kidney cancer accounts for about 3% of cancer deaths and an estimated 51,190 new diagnoses will be made in 2007[1]. Epithelial tumors comprise the majority of kidney tumors and are mainly renal cell carcinomas (RCC). RCC originates in the renal cortex and accounts for up to 85% of malignant kidney tumors. Based on histological classification, approximately 75% of RCCs are of the clear cell type, 15% are papillary, 5% are chromophobic, and the remaining comprise a variety of tumors such as collecting duct tumors and oncocytomas. Poor prognosis of clear cell carcinomas correlates with higher nuclear grade and the presence of a sarcomatoid (spindle cell)

morphology. Papillary and chromophobic carcinomas are associated with a more favorable prognosis than clear cell carcinomas.

Localized RCC (limited to renal parenchyma) is treated with radical nephrectomy with a resulting 5-year survival rate of >80% [2]. Surgical intervention is also considered beneficial for patients with locally advanced disease. Metastatic RCC is typically highly resistant to standard chemotherapy. For many years, surgery and immunotherapy have been the hallmarks of treatment for mRCC. Surgical resection may be appropriate for selected patients, including those with isolated metastases. However, the disease often recurs, even when the primary and metastatic sites are aggressively resected[3]. Even with multimodality therapy, the median survival of patients with metastatic disease remains low at 10-12 months with long-term survival occurring in only 2% of these patients. Radiation therapy can provide significant palliation of painful metastases. [4]

Newer therapies such as tyrosine kinase inhibitors and angiogenesis inhibitors that affect the signaling pathways now make it possible to inhibit specific signals that lead to sustained malignancy. Angiogenesis inhibitors comprise a class of compounds that are being assessed for anti-tumor activity in a variety of tumor types.

Within the past two years, two new drugs have been approved for advanced RCC:

1. Nexavar™ (sorafenib) for improvement in progression free survival compared with control
2. Sutent™ (sunitinib) for improvement in progression-free survival compared with control

Nexavar™ (received regular approval in December 2005):

Sorafenib is a small-molecule inhibitor of VEGFR as well as Raf tyrosine kinase. It was approved for the treatment of patients with advanced renal cell carcinoma (USA) and in Europe for patients who have failed prior interferon or interleukin-2 based therapy or are considered unsuitable for such therapy (EU). In this relapsed population, sorafenib significantly prolonged median progression-free survival (PFS) when compared with placebo (167 days vs. 84 days, respectively) [5].

Sutent™ (accelerated approval January 2006; converted to regular approval in February 2007):

Sunitinib maleate is a small-molecule inhibitor of multiple tyrosine kinase receptors including VEGFR-2. Efficacy in mRCC was established based on objective response rates. In two single-arm studies, objective response rates (ORR) (all partial responses) were 25.5% and 37%. Sunitinib was approved under subpart H (accelerated approval) based upon durable partial responses in two open-label, single-arm, multicenter trials enrolling a total of 169 patients with metastatic disease. All patients had experienced disease progression or intolerance to interleukin-2 and/or interferon-α. The primary endpoint of both studies was overall response rate. At the time of initial marketing approval, the data for progression-free survival and

duration of response were immature, and the confirmatory randomized study comparing progression-free survival in sunitinib to IFN-α was ongoing [6].

In February 2007, the Sutent approval was converted to regular approval based upon the results of the phase 3 trial of 750 treatment-naïve patients with metastatic RCC in which Sutent was demonstrated to prolong progression-free survival over interferon alfa (47.3 weeks vs. 22 weeks). In this study, the overall response rate for Sutent was 27.5% vs. 5.3% with interferon. Information on duration of response and overall survival were not mature at the time of data submission[7].

Proleukin [TM] (aldesleukin/IL2) (regular approval in May 1992)

The cytokine IL-2 exerts indirect anti-proliferative effects by activating cytotoxic T-cells and natural killer cells that directly mediate anti-tumor immunity. High dose IL-2 is approved in the United States for the treatment of mRCC. Approval was based on a 255-patient database with an objective response rate in approximately 15% of patients. Complete responses were seen in ~5% of patients and were often durable. An update of this patient population published in 1998 reported an objective response rate of 19% (CR=9.3%, PR = 9.7%) [8]. The median OS in the initial population of 255 patients with high-dose IL-2 was 16.3 months [9]. This trial was a single arm study with no comparator arm. While IL-2 has been a mainstay for the treatment of mRCC, an overall survival benefit of IL2 in advanced RCC has not been validated due to the lack of randomized, controlled studies comparing IL-2 therapy directly with other therapies. In addition, IL-2 therapy is associated with considerable toxicity, including a 4% treatment-related mortality rate [10] which necessitates inpatient administration and limits its use.

Interferon Alfa

Though interferon alfa does not have marketing approval for the RCC indication in the United States, it has been reported to show survival benefit in mRCC, and it is commonly used in the treatment of advanced RCC. The objective response rate for patients treated with interferon alfa is reported to be 10-15%. A statistically significant 2.5 month improvement (6 months vs. 8.5 months) in overall survival with interferon in metastatic RCC was reported in a randomized, controlled trial conducted in the UK of Interferon-α versus MPA (medroxyprogesterone acetate) [12]. In a study comparing vinblastine in combination with IFN to vinblastine alone, patients on the combination arm experienced a prolonged median overall survival of 15.6 months vs. 8.7 months with vinblastine alone [13].
This repeated demonstration of a survival advantage makes interferon an appropriate and active comparator for this trial.

2.3 Availability of Proposed Active Ingredient in the United States

This is a new molecular entity.

2.4 Important Issues With Pharmacologically Related Products

Temsirolimus is a new molecular entity and is the first m-TOR inhibitor to receive an oncology indication.

2.5 Presubmission Regulatory Activity

10/30/01 Temsirolimus received Fast Track Status for the treatment of RCC following failure of initial therapy.

12/17/01 End of Phase 2 meeting. FDA strongly recommended that Wyeth perform two randomized trials utilizing concurrent controls to support the approval of CCI-779 in the proposed population.

03/04/02 Pivotal Phase 3 study 3066K1-304-WW was submitted for Special Protocol Assessment. In its review, the Division again recommended that Wyeth perform two trials. The Division informed Wyeth that "for a single randomized trial to support an NDA, the trial must be well designed, flawlessly executed, internally consistent across center and efficacy endpoints, and provide statistically and clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication." Agreement was reached on the acceptability of (1) selection of previously untreated patients for the study, (2) the use of IFN-α as a suitable comparator and combination agent), and (3) selection of OS as the primary endpoint.

07/09/04 Temsirolimus received Fast Track Status for the treatment of first-line poor prognosis patients with advanced RCC.

12/16/04 Orphan drug status for the treatment of RCC was assigned.

2/28/05 Pre-NDA discussion held between Wyeth and Division regarding clinical pharmacology and biopharmaceutics program. FDA and Wyeth agreed on items pertaining to the [redacted]. Of significance to this review, FDA informed Wyeth that a completed hepatic insufficiency study report would be needed for NDA submission. Wyeth could not confirm that this would be completed by the time of NDA submission.

10/26/05 Pre-NDA discussion held between applicant and Division regarding QT Evaluation Program. FDA recommended that Wyeth amend their ongoing mantle cell lymphoma study to include ECGs at additional time points after administration, specifically after doses of 175 mg. FDA told Wyeth that the absence of a thorough QT study would not preclude an adequate assessment of risk/benefit at the time of NDA submission.

12/22/05 IND Guidance Teleconference held between FDA and Wyeth to discuss the proposed data format for upcoming NDA.

03/02/06 FDA informed Wyeth that we do not encourage adding an additional interim analysis after an interim look has been performed. However, FDA noted that the overall α was 0.0454 and the second interim analysis was close to the time of the final analysis, and therefore the second interim analysis was deemed acceptable.

4/17/06 Pre-NDA discussion held between applicant and Division regarding Chemistry Manufacturing and Controls. No agreements pertinent to this clinical review were noted.

5/11/06 Pre-NDA discussion held between applicant and Division regarding Pivotal Phase 3 Study Results and Clinical Program. The following clinically important agreements were made in this meeting:

1) FDA agreed that the Wyeth data appear to provide a basis for an NDA submission but that the support of an indication will be a review issue.
2) Wyeth clarified that 5/30/06 would be the cut-off date for the primary analysis.
3) Wyeth agreed to provide a PFS analysis based on investigator assessment and to request a meeting to demonstrate the imaging viewing tool.
4) Wyeth agreed to submit the Safety Update 3 months before the PDUFA date.
5) Wyeth indicated that the hepatic impairment study had a projected completion date of 3Q2007. FDA told Wyeth that if a completed study report cannot be submitted with the NDA, an update to the NDA should be provided to the extent possible in order to construct the best package insert possible.

10/5/06 FDA received NDA 22-088 for temsirolimus for the treatment of advanced renal cell carcinoma.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The clinically pertinent findings from the Chemistry and Microbiology reviews are included below. The reader is referred to the reviews by Dr. Pope (Chemistry) and Dr. Langille (Microbiology) for further details.

Summary of Microbiology Review

Temsirolimus injection and diluent for temsirolimus injection will be [redacted] separate manufacturing facilities. No deficiencies were identified by the microbiology reviewer based upon the information provided. The reader is referred to the microbiology review by Stephen Langille, Ph.D for further details.

Summary of Chemistry, Manufacturing, and Controls Review

Temsirolimus is a New Molecular Entity that is synthesized from rapamycin using conventional synthetic organic reactions and techniques. The Sponsor proposed two drug substance manufacturing sites: Wyeth Pharmaceuticals, Inc. (Rouses Point, NY) [redacted] The pre-approval field investigation of the Rouses Point site resulted in an "acceptable" recommendation from the field and Office of Compliance.

The Sponsor proposed two drug product manufacturing sites. The active concentrate will be manufactured at Pierre Fabre (France), while the diluent for reconstitution will be manufactured at Ben Venue Laboratories (Bedford, OH). An overall "acceptable" EES recommendation was issued by the Office of Compliance on 23-FEB-2007.

The Sponsor proposed, and was granted, a 24-month expiration dating period for the concentrate, when stored under refrigerated conditions (5°C ± 3°C) and protected from light. The Sponsor also proposed a [redacted]-month expiration dating period for the diluent when the material is stored under controlled room temperature for up to 12 months, followed by storage under refrigerated conditions (5°C ± 3°C) for the remainder of the [redacted]-month shelf life. Due to the discrepancy in expiration dating periods for the concentrate and diluent, the approved expiration dating period for the co-packaged drug product is the lesser of the two proposed expiries (24 months), when stored under refrigerated conditions (5°C ± 3°C) and protected from light.

Torisel (temsirolimus) Injection is formulated as a 25 mg/mL sterile solution co-packaged with a specific diluent for reconstitution. The diluent/concentrate combination results in a 10 mg/mL solution that is suitable for further dilution with 0.9% Sodium Chloride Injection for intravenous administration.

From a CMC standpoint, this New Drug Application is acceptable for approval.

3.2 Animal Pharmacology/Toxicology

This section is taken directly from the Animal Pharmacology/Toxicology Review by Haleh Saber, PhD. The reader is referred to Dr. Saber's review for more detail.

Brief overview of clinically pertinent non-clinical findings

Non-Clinical Safety Issues Relevant to Clinical Use
Nutrient availability influences mTOR. mTOR is downstream of multiple pathways, including growth factors, insulin, and nutrients (e.g. glucose). Therefore, while temsirolimus will inhibit mTOR, the increased blood glucose levels (a side effect of temsirolimus treatment) may activate mTOR. This may result in resistance/insensitivity to the initial dose of temsirolimus if hyperglycemia is not controlled. In addition, when controlling the hyperglycemic conditions in patients, insulin may not be an appropriate treatment, as it may activate mTOR.

Although genotoxic signals with temsirolimus were negative and carcinogenicity studies were not conducted with this drug, temsirolimus should be considered carcinogenic in human due to the data available for sirolimus. According to the labeling for sirolimus, the following effects were reported in mice and/or rats in the carcinogenicity studies: lymphoma, hepatocellular adenoma and carcinoma, testicular adenoma. This is not of concern for the proposed indication. Temsirolimus should be considered reprotoxic due to known fetal and embryonic effects.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This NDA was received entirely as an electronic submission available in the Electronic Document Room at \\cdsesub1\evsprod\NDA022088. The regulatory history of this agent was reviewed. No issues were identified during the review that would indicate the need for an ODAC meeting. A review of the submitted studies (3066K1-200-US & 3066K1-304-WW) was performed. The publication in the Journal of Clinical Oncology regarding Trial 200 was reviewed. A literature search for other (non-submitted studies using temsirolimus) was performed. No evidence for any such studies was located. The Clinical Study Reports for Study 304 and Study 200 were reviewed. Electronic raw datasets were analyzed using JMP 6.0 to confirm efficacy and safety conclusions reported by the Applicant. Case report forms provided by the Applicant were reviewed to confirm raw data where appropriate. Raw datasets were used to confirm derived datasets where needed.

The following submissions were received:

- 10/05/06 Original NDA 22-088 submission
- 10/18/06 Amendment to provide supportive documentation for Imaging Database for Trial 304 (randomized, controlled trial)
- 11/16/06 Amendment to provide draft label in Structured Product Labeling (SPL) format
- 11/21/06 Amendment to provide additional supportive documentation for the Imaging Database.
- 11/22/06 Amendment to provide information requested by DSI
- 12/01/06 Amendment to replace previously provided incorrect adverse event data in 11/22/06 submission.
- 12/05/06 Amendment to provide chemistry information regarding stability.

- 12/13/06 Response to requests from Clinical Pharmacology and Pharmacology
- 01/04/07 Provision of Safety Update
- 01/17/07 FDA notified Applicant "In the 'TUMOR' datasets, there are many lesions (568) that were bone lesions. Bone lesions are not considered measurable and cannot be target lesions. How can I differentiate between target and non-target lesions in the Tumor datasets (RAW)?"
- 01/18/07 Applicant responded via email with: "*The variable TUMTYP differentiates between lesion types; target lesions have a value of "Target" and non-target lesions have* a value of "Non-target.

  Please note that in section 18.2.6 in the protocol, there is a provision for measurement of bone lesions if a patient has bone-only disease and a documented measurable target lesion by MRI, with at least 2 osteolytic lesions (one of which is measurable)."
- 01/19/07 Response to CMC Information Request Letter and notification of transfer of sponsor obligations.
- 01/26/07 Response to request for Case Report From from Dr. Prowell
- 01/26/07 Complete Response to CMC Information Request Letter dated 12/19/06.
- 03/02/07 Applicant notified that study report efficacy results could not be confirmed by analysis of derived or raw datasets. Clinical Reviewer provided a list of noted discrepancies between overall response assessment by Independent Radiologist and raw tumor response datasets. Teleconference scheduled for 03/06/07 at 2:30PM
- 03/06/07 Teleconference held with FDA and Wyeth to discuss data discrepancies. Dr. Andrew Strahs informed FDA that when original datasets were divided up into smaller datasets for transmission to FDA, some patient assessments were inadvertently left out. Wyeth to submit corrected raw tumor datasets for review by FDA. Dr. Sun-Mitchell (FDA Statistician) requested datasets with derived variable containing Best Overall Response (from independent radiologist), Duration of Response (independent radiologist), and Clinical Benefit Rate (independent radiologist).
- 03/07/07 FDA received an email from Wyeth indicating that the TUMOR datasets were submitted and clarifying some specifics about the statistical analysis of objective response rates and medians for time-to-event endpoints. In the cover letter attached to the email, Wyeth also stated that they also "determined that the previously submitted Lab Test data sets were missing data. New versions of these Lab Test data sets will be submitted promptly."
- 03/08/07 FDA notified Wyeth via fax that "According to your email with an attached cover letter dated March 7th, 2007, it appears that some safety data sets, specifically Lab Test, are missing data. Please submit these as soon as possible. Depending on the timing of the submission, this may result in a major amendment."
- 03/09/07 Tumor datasets became available for review in the Electronic Document Room.
- 04/05/07 Wyeth submitted additional case report forms that were requested by Tatiana Prowell, MD.
- 04/12/07 Wyeth submitted written responses to FDA labeling comments.
- 04/17/07 Wyeth submitted results of the re-analysis of tumor response data that was requested by the Division.

- 04/30/07 Wyeth submitted information for clarification of bone lesions that were found in the datasets.
- 05/04/07 Wyeth submitted an amendment to a CMC information request.

4.2 Tables of Clinical Studies

Table 4.1 Clinical Studies Using Torisel

Type of Study/# of Subjects	Objective(s) of Study	Study Identifier/Study Design and Type of Control	Test Product(s); Dosage of Regimen; Route of Administration	Type of Subjects	Duration of Treatment
PK/ 12	Evaluation of metabolic profile of temsirolimus	3066K1-133-US /Phase I, open-label, non-randomized, parallel-group	1) Single 25 mg IV dose of temsirolimus (over 30 min) 2) Single 30 mg PO dose	Healthy subjects	Single dose
PK/ Human Metabolism/ 17	Evaluation of the effects of CYP3A4 inhibition on temsirolimus PK	3066K1-148-US/ Phase 1, open-label, non-randomized, 2-period sequential	Period 1: Single dose temsirolimus 5 mg IV Period 2: Single dose each of 5 mg IV (over 30 min) temsirolimus and ketoconazole 400 mg PO daily x7 days	Healthy subjects	Two single doses of temsirolimus Daily x7 dosing of ketoconazole
Human Metabolism/ 26	Evaluation of effects of temsirolimus on CYP2D6-mediated metabolism	3066K1-149-US /Phase 1, open-label, non-randomized, 2-period sequential	Period 1: Single dose 50 mg PO desipramine Period 2: Single dose each of temsirolimus 25 mg IV (over 30 min) and desipramine 50 mg PO	Healthy subjects	Two periods**Study chart states 25mg desipramine dose but protocol and study report say 50mg
Human Metabolism/PK/ 32	Evaluation of effect of CYP3A4 induction on temsirolimus PK	3066K1-151-US /Phase 1, open-label, non-randomized 2-period sequential study	Period 1: Single 25 mg IV (over 30 min.) or 30 mg PO temsirolimus dose Period 2: Single dose of same formulation after rifampin 600mg daily x6.	Healthy Subjects	Two dosing periods
Pharmaco dynamic/ 30	Evaluate the temsirolimus exposure/response relationship using S6 ribosomal kinase in blood	3066K1-145-US /Phase 1, open-label, single-dose, non-randomized, sequential-group exploratory study.	Single dose of 1-25 mg IV temsirolimus via 30 minute infusion	Healthy Subjects	Single dose
Pharmaco dynamic/ 4	Evaluate the effects of temsirolimus on	3066K1-147-US/ Phase 1, open-label, exploratory study	Temsirolimus 25 mg IV (infusion time not provided) once	Adults with newly dx	Three weeks

Type of Study/# of Subjects	Objective(s) of Study	Study Identifier/Study Design and Type of Control	Test Product(s); Dosage of Regimen; Route of Administration	Type of Subjects	Duration of Treatment
	phosphorylation of key proteins in mTOR pathway		weekly for 3 weeks	advanced SCCHN	
Pharmaco dynamic/ 60	Evaluate effect of temsirolimus on the QT interval	3066K1-155-US /Phase 1, single-blind, randomized, 3-period sequential study	Temsirolimus 25 mg IV (infusion time not provided) Placebo Moxifloxacin	Healthy Adults	Unclear from information provided; Period 1: Placebo w/ or w/o single dose moxifloxacin Period 2: Alternate treatment in period 1 Period 3: Single dose temsirolimus 25 mg IV
Safety/ 88 (Part 1 = 63; Part 2 = 25)	Determine MTD	3066K1-100-US/ Phase 1, open-label, 2-part dose-escalation study	Part 1 : Temsirolimus 0.75 to 24 mg/m2 (MTD 14.7 mg/m2 in heavily pretreated patients; MAD 19 mg/m2 in minimally pretreated patients) Part 2: 15 to 37 mg/m2 (30 minute infusion)	Part 1: Adults w/ adv solid tumors not on anticonvulsants Part 2: Adults with recurrent gliomas and taking CYP450 inducers	Once daily for 5 days every 2 weeks 3.8 months maximum
Safety/ 40 (Part 1= 24, Part 2 = 16)	Determine MTD	3066K1-101-EU /Phase 1, open-label, 2-part dose-escalation study	Part 1 : Temsirolimus 7.5 to 220 mg/m2 (MTD 220) Part 2: 220mg/m2 (30 minute infusion)	Adults with advanced solid tumors	Once weekly Total exposure: 14-297 days
Safety/ 26	MTD of temsirolimus and gemcitabine	3066K1-102-US/ Phase 1, open-label, dose escalation study	*Amendment 1:* Temsirolimus (starting dose 15 mg/m2) IV (over 30 minutes) + Gemcitabine 800 mg/m2 IV (over 30 min) on Days 1, 8, and 15 of 28 day cycle *Amendment 2:*	Adults with advanced solid tumors	Weekly x 3 of 28 day cycles Total exposure: 1-28 doses

Type of Study/# of Subjects	Objective(s) of Study	Study Identifier/Study Design and Type of Control	Test Product(s); Dosage of Regimen; Route of Administration	Type of Subjects	Duration of Treatment
			Temsirolimus (starting dose 7.5 mg/m2) IV (over 30 minutes) + Gemcitabine 1000 mg/m2 IV (over 30 min) on Days 1 and 8 of 28 day cycle		
Safety/ 28	MTD of Temsirolimus, 5-FU, and Leucovorin	3066K1-103-EU /Phase 1, open-label, dose escalation study	*Once weekly x6 of 7 week cycles* Leukovorin 200 mg/m2 IV (over 1 hour) starting w/ Day 1 + 5-Fluorouracil 2600 mg/m2 CI Day 1 And Temsirolimus 15-75 mg/m2 over 30 min on D8 of Cycle 1	Adults with advanced solid tumors	6-29 weeks
Safety/ 71	MTD Temsirolimus plus interferon-α	3066K1-124-US /Phase 1, open-label, dose escalation study	Temsirolimus 5-25 mg IV (MTD 15 mg)once weekly plus interferon-α 3 times weekly (6-9 mu thrice weekly)	Adults with advanced renal cell ca with 0-2 prior therapies	3-164 weeks
Safety/ 10	MTD	3066K1-131-JA /Phase 1, open-label, dose escalation	Temsirolimus 15 and 45 mg/m2 once weekly (MTD 15)	Adults with advanced solid tumors	Not provided
Safety/ 20	MTD	3066K1-139-US /Phase 1/2 open-label, 2-part dose escalation study	Part 1: 10-150 mg/m2 (MTD 150) Part 2: 75 mg/m2	Pediatric subjects with refractory solid tumors	1-10 weekly doses
Efficacy and Safety/ 111	Efficacy Safety	3066K1-200-US /Phase 2, randomized, blinded, parallel-group, dose ranging	Temsirolimus 25, 75, or 250 mg IV once weekly	Adults with advance renal cancer (prior therapy or not eligible	1-736 days

Type of Study/# of Subjects	Objective(s) of Study	Study Identifier/Study Design and Type of Control	Test Product(s); Dosage of Regimen; Route of Administration	Type of Subjects	Duration of Treatment
				for IL2)	
Efficacy and Safety/ 28	Efficacy Safety	3066K1-201-US/EU /Phase 2, randomized, double-blinded, parallel-group, dose ranging, placebo-controlled	Temsirolimus 75 or 250 mg OR placebo IV once weekly	Adult men with androgen-independent prostate cancer	Median 9.3 weeks (Minimum time and maximum time not provided in report)
Efficacy and Safety/ 109	Efficacy Safety	3066K1-203-EU /Phase 2, randomized, open-label, parallel-group, dose ranging,	Temsirolimus 75 or 250 mg IV once weekly	Adult women with previously treated locally advanced or metastatic breast cancer	1-60 weeks
Phase 3 Pivotal/ 626	Efficacy Safety	3066K1-304-WW /Phase 3, randomized, open-label, parallel-group, pivotal study	Arm A: IFN-α 3x weekly Arm B: Temsirolimus 25 mg IV weekly Arm C: Temsirolimus 25 mg IV weekly plus IFN-α 3x weekly	Adults with first-line, poor prognosis advanced RCC	1-138 weeks

Reviewer Comment: Applicant Study Report Table 1-1: Clinical Studies of Temsirolimus… contains an error. Study 3066K1-149-US claims that the regimen included "a single dose of 25mg desipramine" during each study period when according to the study report and protocol, each patient received 50 mg of desipramine at each dosing period. Studies 3066K1-200-US and 3066K1-304-WW (highlighted in the above table), were submitted in this application in support of the safety and efficacy of temsirolimus in advanced RCC.

4.3 Review Strategy

The Phase 3 trial was reviewed for safety and efficacy. The Phase 2 trial was used to support the safety of temsirolimus, but not efficacy because it was a dose-finding study, and not a controlled trial. The electronic submission, with the Clinical Study Reports, Summary of Clinical Safety, Summary of Clinical Efficacy, and other relevant portions were reviewed. Major efficacy and safety analyses were reproduced using raw datasets in JMP. A DSI consult was placed for site audits. Trial 200 was published in March 2004 in the Journal of Clinical Oncology[14]. The Phase 3 trial has not been published, except in abstract form.

A literature review was performed on the natural history of renal cell carcinoma, available treatments for RCC, published efficacy trials for RCC, previous FDA Medical Officer reviews for the RCC indication, and any studies published using temsirolimus. No additional information regarding the efficacy or safety of temsirolimus was obtained via literature review.

Consultation was made with clinical pharmacology, pharmacologic toxicology, chemistry, and biostatistics reviewers throughout the review process.

The efficacy review for this application was performed by Virginia Kwitkowski. The safety review was performed by Tatiana Prowell. The synthesis and documentation of overall conclusions were completed by Virginia Kwitkowski and Tatiana Prowell.

4.4 Data Quality and Integrity

The sponsor monitored the study via their Contract Research Organizations whereby qualified clinical monitors would perform site visits at the time of site qualification, initiation, monitoring, and closeout visits. Monitoring generally included the verification of data with source documentation and resolution of discrepancies, ensuring that investigators were fulfilling local regulatory obligations, verification and accountability of laboratory specimens, and the conduction of safety monitoring.

In addition to local monitoring, an independent data monitoring committee (IDMC) reviewed study conduct including accrual/retention of patients, unblinded safety data every 6 months or more frequently if needed. The IDMC also reviewed unblinded efficacy data from 1 planned interim analysis. After this analysis, the protocol was amended to add a second interim analysis. The Applicant sought and received concurrence with this plan from FDA. Decisions regarding early termination of the study for efficacy or lack of benefit were to be made based on results from each of the two interim analyses.

A Division of Scientific Investigations consultation was requested for this Application to evaluate the integrity of the Applicant's data.

Site Selection for DSI Audit

The datasets for the Pivotal Phase 3 trial were queried with regard to the number of patients enrolled per investigator, the presence (or absence) of adverse event reporting from each site, and the ratio of objective tumor responses to the number of enrolled patients from each site. No abnormalities or inequalities were found during this review, so the final site recommendations for DSI audit were based upon the highest enrolling investigators. This way, should problems be identified during audit, the impact upon the review would be greatest.

The following sites were selected for DSI Audit:

Table 4.2: Sites recommended for DSI Audit

Study 3066K1-304-WW		
Investigator	**Site**	**Number of Patients Enrolled**
Piotr Tomczak, MD	Poznan, Poland	26
Jeffrey Sosman, MD	Nashville, TN	15
Michael Carducci, MD	Baltimore, MD	15

As of 3/6/07, all of the four inspections (3 clinical, 1 sponsor) have been completed. Two of the three clinical investigator inspections and the sponsor inspection had some commonly encountered deficiencies that would not preclude approval of the NDA. DSI is awaiting a report from the third clinical investigator inspection. The DSI consult report was filed on 03/12/07. The final classification of the site inspections is still pending, but per DSI conversations with the inspectors, the data provided from the three clinical sites may be used in support of an approval of the submitted NDA.

Reviewer Comment: Inspection results from the Division of Scientific Investigations audits indicate that no undue irregularities were observed in the audited sites.

4.5 Compliance with Good Clinical Practices

The Applicant states in the Study Report that the trial was conducted in accordance with the ethical principles that have origins in the Declaration of Helsinki and in any amendments that were in place when the study was conducted. This study was also designed and performed in compliance with Good Clinical Practice (GCP). Written consent was obtained before enrollment of each patient. The trial was implemented under the IRB/IEC of every participating institution. A moderate number of protocol violations were reported in the application.

4.6 Financial Disclosures

The major randomized, controlled trial is the only study submitted with this application with a design adequate for registration. Per the Applicant's report, 206 investigators participated on the study. According to the Applicant, they did not enter into any financial arrangement with the study clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each investigator was required to disclose to the sponsor of the trial whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b), and none were disclosed.

Reviewer Comment: The trial has a primary endpoint of overall survival which is not typically subject to bias. Secondary endpoints involving tumor response should also not be significantly impacted by bias because blinded tumor assessments performed by an independent radiology firm were used for the formal analyses. No impact on trial outcome related to financial relationships would be expected.

5 CLINICAL PHARMACOLOGY

This entire section is excerpted directly from the Clinical Pharmacology Reviews by Julie Bullock, PharmD and Yaning Wang, PhD. The reader is referred to the Clinical Pharmacology reviews for more detail.

5.1 Pharmacokinetics

The Tmax of temsirolimus typically occurs at the end of infusion (30 mins), and following administration concentrations of temsirolimus decrease in a poly exponential manner with a half-life of approximately 20 hours aver a 25 mg IV dose. The pharmacokinetics of temsirolimus and sirolimus are less than dose proportional with increasing doses and there are no significant differences between the pharmacokinetics in healthy volunteers compared to patients.

5.2 Pharmacodynamics

The primary pathway of elimination of temsirolimus is NADPH-dependent via CYP3A4. Sirolimus was the active metabolite found in blood and plasma and in-vitro studies indicate that temsirolimus and sirolimus exhibit comparable degrees of biologic activity. Drug-drug interaction studies indicate a 56% reduction in sirolimus exposure (AUC), and no effect on temsirolimus exposure when administered with rifampin. Coadministration of IV temsirolimus with ketoconazole did not effect the exposure of temsirolimus but increased the exposure (AUC) of sirolimus by 3.1-fold. In-vitro temsirolimus was considered to be an inhibitor of CYP2D6 and

3A4, however desipramine concentrations were not effected by co-administration with temsirolimus.

5.3 Exposure-Response Relationships

Dose-response was demonstrated for temsirolimus biochemical activity based on a biomarker (p-S6 ribosomal protein activation status in the blood) in healthy male subjects for the dose range of 1 mg to 25 mg single dose. Different results, however, were observed in the two cell types selected, CD3+ and CD19+, with CD3+ showing more prolonged response with larger magnitude (Figure 1). These results were used to support dose selection. In a dose ranging study, no dose-dependence was observed for objective response rate outcomes among 25 mg, 75 mg and 250 mg (Tables 1 and 2). Similar results were observed for time to tumor progression, progression-free survival and overall survival (see table 5.1)

Table 5.1 Tumor Response Rates by Protocol Definition in the ITT Population (N, %)

	Treatment Group			Total
Response	25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	(N=111)
Complete response	0	0	0	0
Partial response	2 (5.6)	1 (2.6)	3 (8.1)	6 (5.4)
Minor response	5 (13.9)	14 (36.8)	10 (27.0)	29 (26.1)
Stable disease [a]	13 (36.1)	11 (28.9)	9 (24.3)	33 (29.7)
Progressive disease	13 (36.1)	10 (26.3)	11 (29.7)	34 (30.6)
Unknown / no data	3 (8.3)	2 (5.3)	4 (10.8)	9 (8.1)

a: Duration of SD had to be at least 8 weeks ± 1 week.

Clinical Pharmacology Conclusions

Significant drug-drug interactions exist with potent CYP3A4 inducers with regards to sirolimus (the primary metabolite of temsirolimus). In the presence of rifampin, sirolimus Cmax decreases by 65%, and AUC decreases by 56%. No change in temsirolimus. Clinical Pharmacology reviewers recommend that strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampicin not be given concomitantly with temsirolimus. If alternative treatment cannot be administered, a weekly intravenous dose of up to 50 mg temsirolimus should be considered.

Significant drug-drug interactions exist with potent CYP3A4 inhibitors with regards to sirolimus. In the presence of ketoconazole, sirolimus Cmax increased 2.2-fold and AUC increased 3.1-fold. No change was seen in Cmax and AUC of temsirolimus. Clinical pharmacology recommends that strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin not be concomitantly administered with temsirolimus. If alternative treatments cannot be administered,

a weekly intravenous dose of 12.5 mg temsirolimus should be considered.

Temsirolimus does not inhibit the metabolism of 2D6 substrates.

Temsirolimus is a P-gp substrate and inhibitor. The current draft guidance recommends that in-vivo evaluation is needed.

Dose reductions of 5 mg/week for toxicity are acceptable, but efficacy has not been established for doses less than 15 mg.

The QT prolongation potential of temsirolimus has not been assessed. A thorough QT study in healthy volunteers is ongoing.

6 INTEGRATED REVIEW OF EFFICACY

This section discusses the clinical review of the design and efficacy of a three-arm, randomized, active-controlled, Phase 3 study which enrolled 626 patients worldwide with poor-prognosis advanced renal cell carcinoma. The data were submitted after the second interim analysis was conducted. The second interim analysis was not pre-specified, but the plan for it was developed and the protocol amended after the first interim analysis. The 2-sided nominal significance level for the additional interim analysis and the final analysis were adjusted at the time of this amendment. The Applicant sought and received FDA concurrence with the plan via a Special Protocol Assessment.

The other study submitted in this application was a randomized, uncontrolled, double-blind, parallel group, dose-ranging Phase 2 study (3066K1-200-US) to evaluate efficacy and safety of varying dose levels (25 mg, 75 mg, or 250 mg) of temsirolimus. This study enrolled 111 patients and was performed in the United States. This study does not provide substantial evidence of efficacy because it does not contain a control group and was intended as a dose-finding study.

The phase 3, randomized, active-controlled trial is the major efficacy trial that provides substantial evidence of the efficacy of temsirolimus in advanced RCC. This section will be primarily focused upon review of this study. For more information on the dose-finding study (3066K1-200-US), the reader is referred to Section 10 (Review of Individual Study Reports).

6.1 Indication

The indication sought by the Applicant is for the treatment of advanced renal cell carcinoma (RCC).

6.1.1 Methods

The clinical data from the major phase 3, three-arm, active-controlled study was used in the efficacy review to support the proposed indication of the treatment of advanced renal cell carcinoma. Efficacy variables examined include the primary endpoint of Overall Survival (OS); and the secondary efficacy endpoints of Progression-Free Survival (PFS), Response Rate (RR), Clinical Benefit Rate, duration of overall response, time to treatment failure, and health outcome

measurements. All of these variables were pre-specified in the protocol and statistical analysis plan. Adjustment of alpha was not made for multiple comparisons. An independent blinded review was conducted for RR and PFS to avoid informed bias.

The submitted data analyses were verified by this reviewer (using JMP 6.0) and the biostatistical reviewer, Dr. Sun-Mitchell (using SAS). A selection of radiologic scans were reviewed for quality assurance.

Per applicant, patients in the study were randomized within 3 geographic regions. Region 1 was the United States (US); region 2 was Western Europe, Canada, and Australia; and region 3 included Asia- Pacific, Eastern Europe, Africa, South America, and other countries. Overall, 184 patients were randomized in region 1, 129 in region 2, and 313 in region 3. Approximately 33% patients in the study were from US.

The group assignment was stratified by nephrectomy status and region.

Reviewer Comment: Overall, the types of protocol violations that were reported do not appear to significantly confound the efficacy or safety analysis. The trial appeared to be conducted in full compliance with Good Clinical Practice. The data from three highly-accruing sites appear to be reliable based upon the DSI inspections. No issues with data quality or integrity at other clinical sites were identified. The Applicant was responsive to Division requests to reanalyze tumor response data once potential protocol violations were identified. The final results after reanalysis appear to be reliable.

6.1.2 General Discussion of Endpoints

Primary Objective

The primary objective of this study was efficacy as defined by a comparison of the overall survival of subjects treated in the three arms. According to the draft Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics published in April 2005, "survival is the gold standard for clinical benefit". This endpoint can be used to support regular approval.

Reviewer Comment: This endpoint does not require blinding because it is not typically subject to bias.

Secondary Objectives

Progression-Free Survival:
While not a direct measure of benefit, progression-free survival can be considered a surrogate for clinical benefit. The correlation between PFS and OS in RCC is not well established. A delay in disease progression may be considered a clinical benefit when progression results in a worsening of disease symptoms. The draft guidance mentioned previously notes that the potential advantages of using PFS as an endpoint are that it reflects tumor growth (which is likely to cause morbidity and death), it can be assessed earlier than survival, and is not subject to confounding by subsequent therapy. Blinding is needed when assessing PFS to avoid investigator bias. Frequent regular assessments of efficacy should be performed symmetrically between treatment groups.

In the phase 3 trial, the assessments appeared to have been performed with equal frequency among groups during the response assessment time period. The PFS endpoint was derived from the independent radiologist assessment of response and progression. During the review, it was determined that the protocol pre-specified response criteria were not followed. The Applicant was asked to reanalyze the response data following the protocol. This reviewer audited the radiology images that were reanalyzed for accuracy.

Nexavar and Sutent received marketing approval for the advanced RCC indication based upon clinical benefit defined by durable PFS. In this Application, PFS is supportive of the primary efficacy endpoint of overall survival.

Objective Response Rate:
Objective Response Rate is defined as the proportion of patients with tumor shrinkage of a predefined amount lasting for a predefined minimum period of time. "The FDA has generally defined ORR as the sum of partial responses plus complete responses. When defined in this manner, ORR is a measure of drug antitumor activity even in a single-arm study." [15]

ORR may be regarded a surrogate for clinical benefit and is supportive of the overall survival primary endpoint in the phase 3 trial.

Clinical Benefit Rate:
Clinical benefit rate (defined in the phase 3 trial as PR + CR + SD $\geq$24 weeks) "incorporates components of time to progression or progression-free survival, which can be captured in a separate measurement." [15]

Duration of Overall Response:
The duration of overall response is usually measured from the time of initial response until documented tumor progression. "The duration of response is considered when taking into account the clinical and regulatory significance of ORR." [15]

Time to Treatment Failure:

Time to treatment failure "is a composite endpoint measuring time from randomization to discontinuation of treatment for any reason (including progression of disease, treatment toxicity, and death). Defined in that way, TTF is not recommended as an endpoint for drug approval because it combines efficacy and toxicity measures." [15]

Safety Analysis
The safety analysis was also a secondary endpoint for the trial. The analysis was to include adverse events, clinical laboratory evaluations, and electrocardiograms. The incidence rates of treatment-emergent adverse events (TEAEs) were to be summarized by treatment group. TEAEs were coded using COSTART and tabulated by preferred term within body system.

Health Outcome Assessments:

Time Without Progression or Toxicity (TWiPT)
The Applicant prospectively proposed to perform a descriptive analysis of group differences in time without progression or toxicity (TWiPT) based upon adverse events and an estimation of patient utilities from the EuroQol EQ-5D questionnaire and evaluation. This analysis proposes to estimate the Quality of Life adjusted survival rates in relation to progression of the disease and toxicity of treatment. Q-TWiPT is derived from Q-TWiST (Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment).

Data Collection Tool:
The EuroQol Group, established in 1987, comprises a network of international, multilingual, and multidisciplinary researchers from several European countries. This group developed the EQ-5D to be a generic measure of health status that is designed to provide a single index value for use as a clinical and economic evaluation of health care and in population health surveys. The EQ-5D has not been shown to provide comprehensive measurement of the "health status" issues of importance to patients with renal cell cancer. Health status is a general term that would require measurement of the multiple domains implied by the term. The EQ-5D is also a composite measure of both safety and efficacy.

Use of Tool:
In the trial, the EQ-5D questionnaire was completed at screening, week 12 visit, week 32 visit, any visit at which a symptomatic NCI CTC grade 3 or 4 adverse event was recorded (if possible, unless medical condition is prohibitive), and the withdrawal visit. This assessment consisted of the EuroQol EQ-5D questionnaire and evaluation. This schedule uses the tool at multiple time points when, in fact, it is designed for use at a single time point.

Bias:
In this trial, this assessment is subject to observer bias because of the unblinded nature of group assignment. It is also possible that the time with grade 3 or 4 toxicities may be overestimated, and the symmetry between treatment groups is not known.

Missing Data:

Missing data casts doubt on study results. At baseline EQ-5D assessment, 605/626 patients completed the tool. The prevalence of a missing baseline assessment is not evenly distributed between the groups. In the IFN-α/Temsirolimus group, 4% were missing; in the IFN-α alone group, 4% were missing, and in the temsirolimus alone group, only 1% were missing).

Per the Applicant report, 260 of 300 patients completed the assessment at withdrawal due to disease relapse. This reviewer analyzed the raw data and found that there were 340 patients who completed the EQ-5D assessment at the withdrawal visit. The assessments were not evenly distributed between treatment groups, with the IFN-α/temsirolimus group submitting 108, IFN-α alone group submitting 106, and temsirolimus submitting the most at 126. At subsequent visits 1-11, between 3 and 21 assessments were obtained. In general, the treatment groups were symmetrical with regard to which patient submitted a completed tool at these non-planned timepoints. Imputed values for missing data were not utilized.

Confounding Variables:
The improvement in time without progression or toxicity may be confounded by changes in concomitant medications. Medications prescribed to treat toxicity should reduce the toxicity symptoms. No analysis of the possible effect of concomitant medications was submitted by the Applicant. The statistical plan did not address the issue of multiple comparisons. The plan also did not define what magnitude of difference between groups would be considered clinically relevant.

Reviewer Comment: The health outcomes assessment of QTwiPT/QTwiST is a composite endpoint of both safety and efficacy. No evidence of the validation of this tool in the RCC population or treatment indication was provided by the Applicant. The EQ-5D is being used in a setting for which it is not designed, and more frequently than intended. The use of concomitant medications may confound the results of this analysis. The baseline data tool was missing in 3.4% of the patients, and missing data were not evenly distributed between the treatment arms. Patient reported outcomes are subject to bias in open-labeled trials. A detailed and prospectively planned Statistical Analysis Plan for this data was not provided. Of particular concern are the lack of a plan for Bonferroni's correction for multiple comparisons and an estimation of a clinically important difference between groups. [redacted]

Caregiver Assessment
The patient's primary caregiver was asked to participate in a personal assessment and was presented an informed consent form. Upon voluntary signature, the screening assessment was presented for completion if the caregiver was able to understand a written survey in an available language. This caregiver was asked to complete the questionnaire every 4 weeks for the first 32 weeks of the patient's treatment. This continued as long as he or she remained the primary caregiver or until premature withdrawal of the caregiver or patient for any reason.

Reviewer Comment: Using the Caregiver Outcomes Assessment, the recall period is from immediate to one week ago. The Applicant has not provided data to support the validation of this tool in this population. No information from the caregiver assessment is included in the Applicant's proposed label.

Biochemical Correlational Work
In addition, subject responses across all 3 treatment arms were to be evaluated based on screening tumor expression of proteins involved in AKT-mTor pathway (i.e., Akt phosphorylation, PTEN expression).

Reviewer Comment: These biochemical endpoints are considered exploratory and have no current impact on the efficacy analysis.

6.1.3 Study Design

The study is an ongoing, randomized, multi-center, international, open-label study comparing temsirolimus to temsirolimus plus interferon-alfa and interferon-alfa alone in the treatment of poor prognosis, advanced renal cell carcinoma patients.

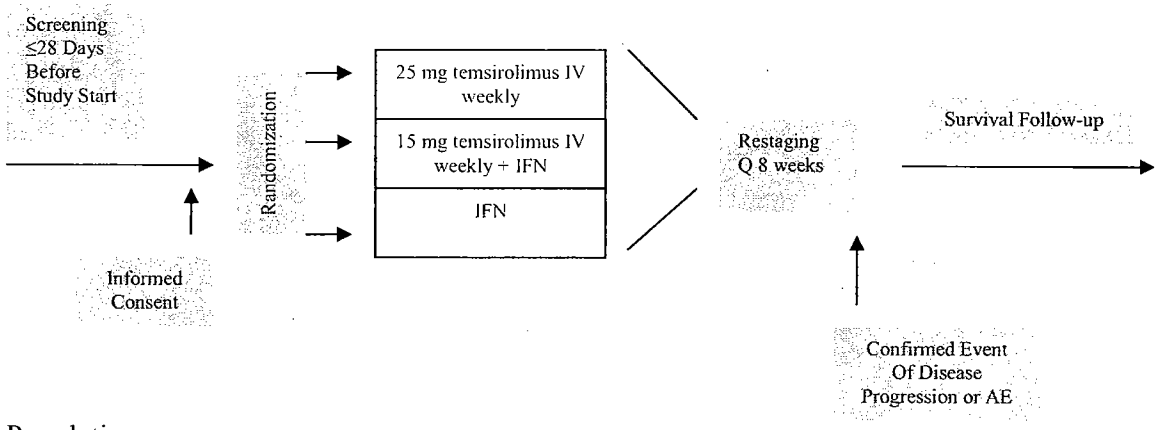
Six hundred and twenty-six patients with advanced RCC without a history of prior systemic anti-cancer treatment were randomized to one of the three arms:

- Interferon alfa 3 MU SC 3x weekly for the first week, 9 MU SC 3x weekly for the second week, 18 MU SC 3x weekly thereafter (N=207)
- Temsirolimus 25 mg IV weekly (N=209)
- Interferon alfa (3 MU 3x weekly for one week followed by 6 MU subcutaneously three times weekly + temsirolimus 15 mg IV weekly (N=210). If either the temsirolimus or IFN-α doses were not tolerated in either treatment arm, dose modification was permitted.

The subjects were stratified by prior nephrectomy (Yes or No) and region (1= US, 2= Western Europe, Australia and Canada, and 3= other [Asia-Pacific, Eastern Europe, Africa, South America]). The purpose of this stratification is to ensure that the stratum are equally distributed among the groups. The US region was divided evenly between the temsirolimus, interferon, and temsirolimus + interferon arms with 61, 61, and 60 patients respectively. The Western Europe/Australia/Canada region was divided evenly between the temsirolimus, interferon, and temsirolimus + interferon arms with 44, 43, and 42 patients respectively. The Asia region was divided evenly between the temsirolimus, interferon, and temsirolimus + interferon arms with 104, 103, and 106 patients respectively. Patients who had undergone prior nephrectomy were evenly divided between the temsirolimus, interferon, and temsirolimus + interferon groups with 139, 139, and 141 patients respectively. Patients who had not undergone prior nephrectomy

were evenly divided between the temsirolimus, interferon, and temsirolimus + interferon groups with 70, 68, and 69 patients respectively.

Figure 6.1: Trial Design of the Randomized, Three-Arm, Active-Controlled Study



Population:
The study population was patients with histologically confirmed, advanced (Stage IV or recurrent disease) RCC who had not received prior systemic therapy for their disease.

Other Inclusion Criteria:
1. Patients were required to have at least 3 of the following 6 prognostic factors indicating a poor prognosis:

- <1 year from time of initial RCC diagnosis to randomization
- Karnofsky performance status of 60 or 70
- Hemoglobin less than the lower limit of normal (LLN)
- Corrected calcium >10 mg/dL
- LDH >1.5 times the upper limit of normal (ULN)
- >1 metastatic site of disease [sites defined as different tissues with metastasis: lung, liver, bone, kidney, lymph node, etc.] (added during amendment number 2)

2. Karnofsky score ≥ 60 (added during Amendment 1)
3. Measurable disease as per RECIST (Amendment number 1 allowed for patients with bone only disease per RECIST criteria.)
4. Age ≥ 18 years
5. Marrow function: ANC ≥ 1500 cells/mm3 and hemoglobin ≥ 8.0 g/dL
6. Adequate renal function (serum creatinine ≤ 1.5x ULN)
7. Adequate hepatic function (bilirubin ≤ 1.5x ULN, AST ≤ 3x ULN [≤ 5x ULN if liver metastases present]
8. Fasting serum cholesterol ≤ 350 mg/dL, triglycerides ≤ 400 mg/dL
9. Subjects receiving CYP450 3A4 inducers or inhibitors must be on stable doses for at least 1 week prior to randomization.

10. Life expectancy of at least 8 weeks.
11. Signed and dated informed consent form.

Exclusion Criteria:

1. CNS metastases. (May be eligible if prior history of CNS metastases were treated with either RT or surgical resection ONLY and subjects are asymptomatic, with stable disease and not requiring steroids. (Amendment number 1 allowed for patients with stable, asymptomatic CNS metastases).
2. Prior anticancer therapy for RCC. [Subjects are eligible if they had nephrectomy and/or radiation therapy but not systemic therapy for RCC].
3. Prior investigational therapy/agents within 4 weeks of randomization.
4. Prior history of other malignancy within 5 years other than basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ.
5. Not recovered from prior surgery and/or surgery or radiation therapy within 4 weeks of randomization.
6. Immunocompromised subjects, including subjects known to be HIV positive, Hepatitis B positive, or carriers of Hepatitis B or C. Subjects who are Hepatitis B/C antibody positive are eligible as long as they are antigen negative.
7. Active infection or serious intercurrent illness.
8. Presence of unstable angina or myocardial infarction within 6 months, use of ongoing maintenance therapy for life-threatening arrhythmia, known pulmonary hypertension, or pneumonitis.
9. Pregnant or nursing women, women of childbearing potential who are not using a medically acceptable contraceptive device, or men who are not using a medically acceptable form of contraception with partners of childbearing potential.
10. Any other major illness that will increase the risk associated with participation.
11. Known hypersensitivity to any of the components in temsirolimus infusion of IFN-α product or other medical reasons for not being able to receive adequate pre-medications (antihistamine or anti-inflammatory agents).

Tumor Assessment
The patients received their assigned treatment until tumor progression or unacceptable toxicity. Radiographic tumor evaluations (CT of the chest/abdomen/pelvis) were performed within 4 weeks before randomization and then every 8 weeks until disease progression (even after stopping test article). Radionucleide bone scans were required at screening and at the end of the study. Plain radiographs of the bone scan abnormalities were required at screening, every 8 weeks during treatment and post-treatment, and at the end of the study. The investigator was responsible for recording tumor measurements and response evaluations on the patient's CRF.

Independent Radiology Review
To minimize the possibility of investigator bias, the original films were also sent to a central imaging service provider for a blinded independent review by two radiologists. All response endpoints were assessed by the independent radiology review for patients who had a baseline and

at least one follow-up scan. Bias was minimized in the independent review by only providing the reviewer with the patient's surgical and radiation treatment history.

The technique used in the independent review was as follows:

- Readers separately reviewed baseline films and all post-treatment films in random order.
- Disagreements regarding overall response or date of progression between readers were resolved by a third radiology reader (adjudicator) who decided which reader was correct.
- The independent readers applied the same criteria as the investigator to determine baseline tumor burden, tumor response at each assessment, and best overall response.

Reviewer Comment: The design of this trial meets the FDA criteria for substantial evidence of efficacy based on the definition of an adequate and well-controlled trial per CFR 314.126. The sponsor made a clear, pre-specified statement of the study objectives and of the proposed methods of analysis. The study used a design of active treatment concurrent control with an appropriately selected comparator. Patients were randomized to their group assignment, but blinding was not necessary to achieve bias avoidance as the primary endpoint (OS) is not subject to bias. The response assessments were performed by blinded reviewers to avoid bias between treatment groups for tumor response-related endpoints (PFS, ORR, OR duration). The initial application provided a tumor response analysis that varied from the protocol plan. The data was reanalyzed according to protocol specified RECIST-based criteria at FDA request. The re-analysis did not lead to significant changes in proposed labeling claims.

Protocol Landmarks:

Original Date of Protocol: 27 March 2003

First Patient Randomized: 30 July 2003

Amendment 1: 06 January 2004

Major changes were:
1. Revised the eligibility criteria to allow for enrollment of patients with a Karnofsky performance status of ≥ 60.
2. Allowed for the enrollment of patients with stable, asymptomatic CNS metastases.
3. Clarified the eligibility criteria for patients with bone-only disease per RECIST criteria.
4. Eliminated the requirement for a pump to infuse temsirolimus.
5. Changed the scheduled time point for Quality of Life and Caregiver assessments from week 24 to week 32.
6. Implemented CTC version 3.0 to assess the severity of adverse events.

Amendment 2: 15 March 2004

Major changes were:
1. Adjusted the number of deaths required to be observed/expected in the statistical analysis plan. (Changed from using the number of deaths in IFN-α arm to using the total number of deaths in the study.)
2. Added a sixth prognostic factor of more than 1 site of metastasis.
3. Removal of the sentence from section 15.1.1 that read "In addition, the assessment of causality of adverse events is more difficult if administration is on the same day." As AE causality is assessed in relation to the combination, this statement was no longer applicable.
4. Clarification of causal relationship between adverse events and test article.
5. Expansion of QoL questionnaire.

Amendment 3: 14 September 2004, US and Canada

Major changes were:
1. This site-specific amendment for selected sites in the US and Canada provided for the collection of ECGs (in triplicate) at the following time points during dose 1, cycle 1 for all 3 study arms:
   - Immediately post administration of pretreatment administration
   - Immediately prior to the end of infusion of temsirolimus (Arm B or C) or immediately after the end of administration of IFN-α (Arm A), as appropriate.
   - Three (3) months following the first dose, immediately prior to the end of infusion of the respective treatment. The results were to include heart rate and rhythm, and PR, QRS, QT, and QTc intervals.

First Interim Analysis : Dataset cutoff 05 April 2005; Data reviewed 11 April 2005
Performed after 239 deaths had occurred. Discussion with FDA occurred, and FDA concurred with the plan for a second interim analysis.

Amendment 4: 10 March 2006
Major changes were:

1. Incorporated an additional interim analysis and modified the number of deaths for the primary analysis after discussions with regulatory authorities.
2. Clarification that the secondary objective of clinical benefit defined as CR, PR, or SD for at least 24 weeks.

Second Interim Analysis Performed: 28 March 2006
Data cutoff: 15 March 2006
Performed after 442 deaths had occurred.

The Independent Data Monitoring Committee (IDMC) advised Wyeth that the protocol-specified analysis of Overall Survival had crossed the O'Brien-Fleming boundary for the comparison of temsirolimus alone versus interferon. At that time, the IDMC approved the release of the

current study to the sponsor. This application provides the interim clinical study report for the phase 3 study. The data cutoff for this application is 30 May 2006.

Appears This Way
On Original

Reviewer Comment: Amendment 1 had a major impact on the analysis of the secondary tumor response endpoints of ORR, PFS, TTR, and duration of response (DOR). Amendment 1 allowed patients with lesions that are not considered measurable (by RECIST) to be measured and followed for response. In addition, the radiological evaluations that were performed then deviated from the pre-specified response assessment per protocol by measuring bone lesions in patients who had other measurable soft tissue disease. This amendment was not part of the Special Protocol Assessment and was not agreed upon by the FDA. The FDA asked the Applicant to reanalyze their response data and resubmit to the agency for review. The only endpoint calculation that was altered after the re-analysis was the PFS of one patient on the IFN-α/temsirolimus arm. The response re-analysis, however, did not appear to have significantly changed any of the efficacy endpoints pertinent to labeling claims. The statistical analysis plan did not provide for adjustment of alpha for multiple comparisons for secondary endpoints. For this reason, the p-value cannot be compared to 0.05.

The Phase 2 dose finding study (Study 200) established that antitumor activity similar to or greater than historical efficacy of IFN-α or IL-2 in patients with RCC was seen in all three dose levels studied (25mg, 75mg, and 250mg). In addition, treatment emergent adverse events, grade 3 or 4 TEAEs, and serious adverse events (SAEs) were similar in the three dose groups. However, a trend toward more dose reductions at the higher dose levels due primarily to thrombocytopenia and mucositis was noted. For these reasons, the lowest dose of 25mg IV weekly was selected for Phase 3 evaluation.

Study Conduct

The duration of the study was adequate and controlled by the time to progression and survival of each individual patient. The entry criteria were appropriately restrictive to assure safety and the ability to generalize the efficacy findings. The trial targeted a seriously ill population by selecting patients with at least a minimum number of negative prognostic factors. The secondary efficacy endpoints of Progression Free Survival and Response Rate were based upon an independent and blinded radiology review.

An Independent Data Monitoring Committee (IDMC) reviewed data from 2 interim analyses. The first interim analysis was pre-specified and occurred after 239 deaths, and the second occurred after 442 deaths. When the second interim analysis was added, the critical p-value was adjusted to preserve an overall 5% significance level. For the final analysis after approximately 504 deaths, the O'Brien-Fleming boundary is 0.0211.

6.1.4 Efficacy Findings

Primary Analysis Population

The primary efficacy analysis for this review was just after the second interim analysis with a data cutoff of 30 May 2006. As of the data cutoff, 626 patients had been randomized and comprised the intent-to-treat (ITT) population for the primary analysis of OS (overall survival).

Two-hundred and ten patients were randomized to the IFN-α + temsirolimus arm, two-hundred and seven patients were randomized to the IFN-α-only arm, and two-hundred and nine patients were randomized to the temsirolimus-only arm. Seven patients (3%) randomized to IFN-α, one patient (0.5%) randomized to Temsirolimus, and two patients (1%) randomized to interferon + temsirolimus withdrew prior to receiving treatment. After the second interim analysis, the study continued to treat all patients that were currently receiving treatment on study.

Trial Eligibility and Baseline Characteristics

The eligibility criteria are discussed in detail in section 6.1.3. It is important to highlight that this trial studied a previously untreated population with advanced disease with a minimum of 3 out of 6 pre-specified poor prognostic indicators. This study population was selected due to their expected short life expectancy to evaluate whether temsirolimus could prolong overall survival when compared to standard treatment for renal cell carcinoma. This study population mirrors the general RCC population, as approximately 25% of patients are metastatic at presentation. The major differences between the general RCC population and the study participants are that the study excluded patients with significant cardiovascular, hepatic, or renal co-morbidities, symptomatic central nervous system metastases, active infection, or recent major surgery. These conditions are seen in clinical practice.

Demographics of Study Population

Table 6.1: Baseline Demographics of ITT Population (Reviewer Analysis)

Variable	Temsirolimus N=209	IFN-α N=207	IFN-α + Temsirolimus N=210
Gender, n (%)			
Male	139 (66.5)	148 (71.5)	145 (69)
Female	70 (33.5)	59 (28.5)	65 (31)
Race, n (%)			
White	186 (89)	191 (92.3)	193 (91.9)
Black	9 (4.3)	8 (3.9)	8 (3.8)
Asian	6 (2.9)	4 (1.9)	3 (1.4)
Other	8 (3.8)	4 (1.9)	6 (2.9)
Age, years			
Median	58	60	59
Mean	58.7	59.2	59.3
Range	32-81	23-86	32-82
Performance Status , n (%) (Karnofsky)*			
50-60	8 (3.8)	23 (11.1)	21 (10)
70-80	183 (87.5)	169 (81.6)	176 (83.8)
90-100	17 (8.1%)	4 (1.9)	12 (5.7)

Variable	Temsirolimus N=209	IFN-α N=207	IFN-α + Temsirolimus N=210
Region, n (%)			
1	61 (29.1)	61 (29.4)	62 (29.5)
2	44 (21)	43 (20.7)	42 (20)
3	104 (49.7)	103 (49.7)	106 (50.4)
Prior Nephrectomy n (%)			
No	70 (33.5)	68 (32.9)	69 (32.9)
Yes	139 (66.5)	139 (67.1)	141 (67.1)

*Numbers may not add up to 100% because one patient from each group had a missing value for baseline Karnofsky.

Baseline Assessment

Prior to the onset of study treatment, patients underwent medical history and physical examination, evaluation of inclusion and exclusion criteria, query of past and present medications, tumor pathology confirmation, radiographic examinations, performance status assessment, informed consent, vital signs measurement, ECG, chest x-ray, urinalysis, CBC with differential, fasting chemistries, coagulation tests, pregnancy test (where appropriate), Euroqol EQ-5D questionnaire, and completion of a caregiver assessment by the patient's primary caregiver.

On-Study Evaluations

Clinic visits occurred weekly for all three arms of the study. Day 8 and 22 clinic visits were omitted for the IFN-α arm patients after 16 weeks if clinically appropriate. Physical examination, performance status assessment, ECG (US & Canada only), coagulation tests, and caregiver assessment occurred every four weeks and at the withdrawal visit. CBC with differential was obtained at least weekly for 16 weeks, subsequently reduced to every 2 weeks if clinically appropriate. If patients were receiving anticoagulant therapy, their coagulation parameters were monitored weekly for 4 weeks, and then per protocol. Clinical chemistries were obtained every 2 weeks until week 16, at which time the frequency was reduced to monthly if clinically appropriate. Vital signs were obtained every four weeks and before each temsirolimus administration. Concomitant medications and adverse event monitoring occurred continually throughout study drug administration. The EuroQol EQ-5D was to be completed at baseline, week 12, week 32, any visit which a symptomatic CTC grade 3 or 4 adverse reaction was recorded, and the withdrawal visit.

Radiographic Evaluations

CT scans of the chest, abdomen, and pelvis were required by protocol at baseline (within 4 weeks before randomization) and every 8 weeks starting from randomization (not adjusted based on treatment delays) until disease progression. Scans were also performed at the withdrawal visit if they had not been done within 4 weeks before discontinuation and at the time of response

confirmation. Scans were continued after study treatment ended until disease progression was observed, new anticancer treatment was initiated, or death occurred.

CT or MRI of the brain was required at screening and at withdrawal if the patient had known brain metastases. Radionuclide bone scans were required at screening and at withdrawal or confirmation of response (if a previous site of active disease). Plain radiographs of bone scan abnormalities were required at screening, every 8 weeks during the treatment period, post-therapy every 8 weeks, at withdrawal, and at confirmation of response if a prior site of disease activity.

The initial protocol version stated that RECIST tumor response criteria would be followed. RECIST criteria clearly states that bone lesions are not measurable and not to be considered target lesions. Amendment 1 allowed the enrollment of patients with bone-only metastasis and proposed to measure their bone lesions by MRI. During the review of the application, it was noted that the protocol was violated in the following ways with regard to response assessments:

- Not all patients with bone-only disease underwent MRI for bone lesion measurement
- Some patients, who otherwise had RECIST-defined measurable disease, had bone target lesions recorded in the database and used in the response assessment.

FDA noted these protocol violations and requested that the Applicant re-analyze tumor lesions per protocol. This required the recalculation of their PFS, ORR, DOR, TTR endpoints. This re-analysis altered the date of progression for one patient in the IFNα/temsirolimus arm and shortened the PFS duration of that arm by 0.2 months.

Post-Therapy Follow-Up

Following the cessation of study drugs (for toxicity, progression of disease, or other reasons), subjects were followed every 2 months for anticancer therapies received, date of death/cause of death, and date of disease progression. This information was either collected in person or via telephone interview. Adverse events were captured for 15 days after cessation of therapy. Any SAEs that were believed related to temsirolimus therapy were reported after this 15-day period.

Handling of Missing Data

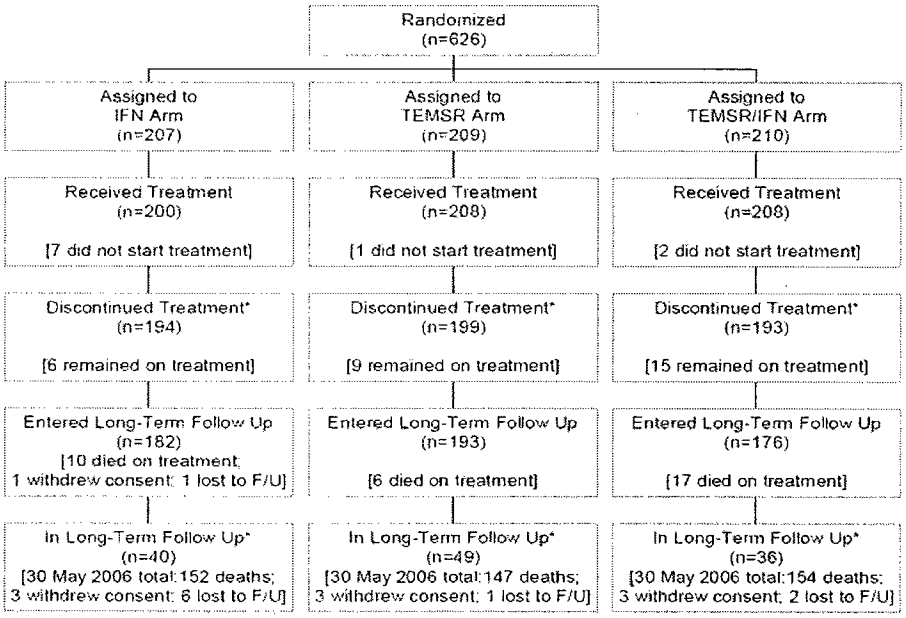
Methods for handling missing or incomplete tumor assessments were as follows:

- Lesions "too small to measure" were considered to have a size of 5 mm.
- If a single lesion split into 2 smaller lesions, the sum of the longest diameter of the 2 smaller lesions was used as the longest diameter for the original single lesion.
- If tumor assessments intended for the same visit were performed at different dates, the latest date of the tumor evaluations was considered the date of the tumor assessment unless the assessment was PD (in which case the earliest date of tumor evaluation was considered the date of PD).
- For any missing scheduled non-target lesion assessment between 2 valid non-target lesion assessments of SD, the non-target lesion was considered to show SD.

• If the target lesion assessment was PR or SD and the non-target lesion assessment was either incomplete or not documented, the overall response was considered to be PR or SD, unless the investigator had observed symptomatic deterioration.

For analysis of OS, patients not known to have died were censored on the last date they were known to have been alive. For PFS analysis, the date of progression for patients not known to have died or had PD was censored on the date of the last valid post baseline tumor assessment or at the randomization day, if no valid tumor assessment was performed post baseline.

Figure 6.2: Disposition of Randomized Patients (Applicant Figure)



Protocol Violations

A moderate number of protocol violations were reported in the application. However, the Applicant did not provide a representation of how frequently the violations occurred in each arm. This information was requested from the Applicant on 03/23/07. The Applicant states that none of the protocol violations were considered major or having potential to confound the efficacy or safety analyses. More protocol violations were noted by the reviewer regarding the application of the pre-specified response analysis. Review of the submitted datasets indicated that patients with metastasis limited to the bone had not been imaged by MRI as required by the protocol. In addition, lesions labeled as "bone" were included in the tumor datasets for patients who had measurable soft tissue disease. The Applicant was asked to perform a reanalysis of the tumor response data to follow the protocol.

Table 6.2

Summary of Protocol Violations By Treatment Arm			
Treatment Arm	**Failed to Meet Entry Criteria**	**Received Concomitant Anticancer Therapy**	**On Treatment >30 Days After Disease Progression**
IFN-α	17	11	1
TEMSR	28	14	13
IFN-α\ TEMSR	15	13	11
TOTAL	**60**	**38**	**25**

Among the 71 patients who failed to meet the study entry criteria, 45 of them did not meet the entry criteria based on the information reported on the inclusion or exclusion CRFs. The reasons for not meeting the criteria were as follows:

- Laboratory abnormalities beyond the protocol specified guidelines = 17 patients
- <3 prognostic factors = 17 patients
- Brain metastases with symptoms = 4 patients
- Radiation therapy or surgery not within the timeframe set forth in the protocol =3 patients
- Prior systemic therapy = 3 patients
- Did not meet the Karnofsky performance status required = 1 patient
- Active infection = 1 patient
- Prior malignancy within 5 years = 1 patient
- Prior investigational therapy/agents within 4 weeks of randomization = 1 patient

Among the 71 patients who failed to meet the study entry criteria, 26 of them were identified as having failed to meet the study entry criteria based on review of additional clinical data. The reasons for not meeting the criteria were as follows:

- Failed to meet protocol-specified laboratory values = 9
- <3 poor prognostic factors at time of randomization = 6
- Active infections = 3
- Failed to meet KPS criteria = 2
- Brain metastases = 2
- Not recovered from radiation therapy =1
- Unstable angina or myocardial infarction = 1
- Had received prior anticancer therapy for RCC = 1
- Did not have histological or cytological confirmation of advanced RCC = 1

Reviewer Comment: The patients enrolled were evenly distributed to the three treatment groups by age, gender, and race. There does appear to be a greater number of patients with a higher functioning Karnofsky score in both temsirolimus-containing arms as compared to the interferon arm (8.1% TEMSR vs. 5.7% IFN-α/TEMSR vs. 1.9% IFN-α). It is also noted that the temsirolimus arm had a much lower percentage of patients with a lower functioning Karnofsky score (3.8% TEMSR vs. 11.1% IFN-α vs. 10% IFN-α+TEMSR). This inequality between groups may put the temsirolimus-containing groups at a survival advantage over interferon. The groups were stratified by region and prior nephrectomy, so the groups, not surprisingly, did not vary in these characteristics.

Prognostic Factors

The patient population in this study was prospectively defined based on having at least 3 of 5 (initial protocol) or 3 of 6 (after amendment 2) poor prognostic factors. The prognostic factors included the 5 factors in the Memorial Sloan-Kettering Cancer Center (MSKCC) classification system plus the presence of more than 1 site of metastatic disease. The percentage of patients with a specific number of prognostic factors was similar in the 3 treatment arms. This model has been retrospectively demonstrated to correlate with survival in advanced RCC (Mekhail et al., JCO, 23(4), Feb 2005).

Table 6.3: Number of Prognostic Factors by Arm (Reviewer Analysis)

Number of Prognostic Factors Per ITT Population (%)						
Arm	**1 of 6**	**2 of 6**	**3 of 6**	**4 of 6**	**5 of 6**	**6 of 6**
TEMSR	0	6.7	34.9	42.1	15.8	0.5
IFN-α	1	4.3	28.5	45.9	18.8	1.4
TEMSR + IFN	0	5.7	31	45.2	16.2	1.9

Reviewer Comment: 5.3 % of patients randomized to IFN, 6.7% of patients randomized to Temsirolimus, and 5.7% of patients randomized to Temsirolimus + IFN were not eligible because they had too few prognostic factors. This protocol violation is relatively evenly distributed among the treatment groups, therefore not confounding evaluation of the study results.

Efficacy Results

Overall Survival

At the time of data cutoff for this application, 446 (71%) of the 626 patients in the ITT population had died. Censoring dates were used for the other 180 patients. The reasons for censoring are provided in Table 6.4 below. The results are provided in Table 6.5.

Table 6.4: Reasons for Censoring in Overall Survival Analysis in ITT Population (Applicant Table)

	Temsirolimus N=209	IFN-α N=207	Temsirolimus + IFN-α N=210	TOTALS
Any reason, n (%)	66 (31.6)	58 (28)	56 (26.7)	180 (28.8)
On treatment	14 (21.2)	8 (13.8)	15 (26.8)	37 (20.6)
Alive and in follow-up	49 (74.2)	40 (69)	36 (64.3)	125 (69.4)
Lost to follow-up	3 (4.5)	10 (17.2)	5 (8.9)	18 (10)

Reviewer Comment: The proportion of patients who were censored for any reason was evenly distributed among treatment arms. A moderate difference was observed in the proportion of patients who remain on treatment (with the combination arm and Temsirolimus arm having more than interferon alone) as a reason for censoring. The proportion of patients who were alive and in follow-up as a reason for censoring did not vary significantly between groups. The proportion of patients who were lost to follow-up as a reason for censoring did vary significantly with more patients in the interferon arm lost to follow-up compared to temsirolimus or combination arms.
The datasets indicate that a few patients withdrew consent specifically because they were randomized to receive interferon alone. This explains the inequality between groups. The datasets were queried for other possible reasons for withdrawal of consent or loss to follow-up, and no patterns were identified. Overall, this amount of censored data for overall survival does not vary significantly between groups and probably does not confound the analysis.

Table 6.5: Median Survival Data by Treatment Group in ITT Population (Reviewer Table)

	Temsirolimus N=209	IFN-α N=207	Temsirolimus + IFN-α N=210
Median Survival in months	10.9	7.3	8.4
HR	0.73	--	0.96
95% Confidence Interval	(0.58, 0.92)	--	(0.76, 1.20)
log-rank p-value	0.0078	--	0.6965

Overall survival was evaluated by the reviewer in the ITT population (data source: DEATH and RANDOM raw data sets) using the JMP 6.0 program. No significant variations were noted between reviewer analyses and applicant analyses during this evaluation. The biostatistical reviewer was also able to replicate the Applicant analyses using the derived datasets and SAS program.

One variable that could confound survival analyses is any variation between treatment arms of the timing of the patient's last contact before a dataset cutoff date. An analysis was undertaken in order to determine any variations between arms. This reviewer determined that among the patients whose last contact date was before the data cutoff, 74% of the IFN-α arm, 75% of the Torisel arm, and 81% of the IFN-α+Torisel arm had contact dates within 2 months of the dataset cutoff date of 03/15/06. The two month time point is pertinent because the protocol specified this frequency of contact for survival data collection. Among the patients whose last date of contact was > 2 months before the dataset cutoff date, 38% in the IFN-α arm, 67% in the Torisel arm, and 60% in the IFN-α+Torisel arm had withdrawn consent, prohibiting the investigators from contacting them for follow-up information.

Subsequent Therapy

Therapies that patients received after discontinuing treatment with the study drug(s) for this trial have the potential to impact overall survival. According to the Applicant analysis of subsequent anti-cancer therapy, 48 patients in the temsirolimus group, 15 patients in the interferon group, and 18 patients in the temsirolimus + interferon group went on to receive interferon after completion of the study. This reviewer queried the submitted data for this information, but the results varied from that of the Applicant. The Applicant was contacted on 04/24/07 regarding the discrepancy. The Applicant responded (on 4/25/07) that the raw data table containing the subsequent therapies only contained the first regimen taken after discontinuing study drug therapy and that the entire list of subsequent anticancer therapies could be found in Table 8.4-1 in the Clinical Study Report-64508. Therefore, if a patient was treated first with bevacizumab and then interferon, only bevacizumab would appear in the raw data table. The differences

between the numbers of patients taking interferon after the study did not vary significantly between the raw table and the Table 8.4-1 from the CSR-64508, so the results are probably reliable. Table 6.6 below provides the Applicant analysis of select anticancer therapies taken during long-term follow-up.

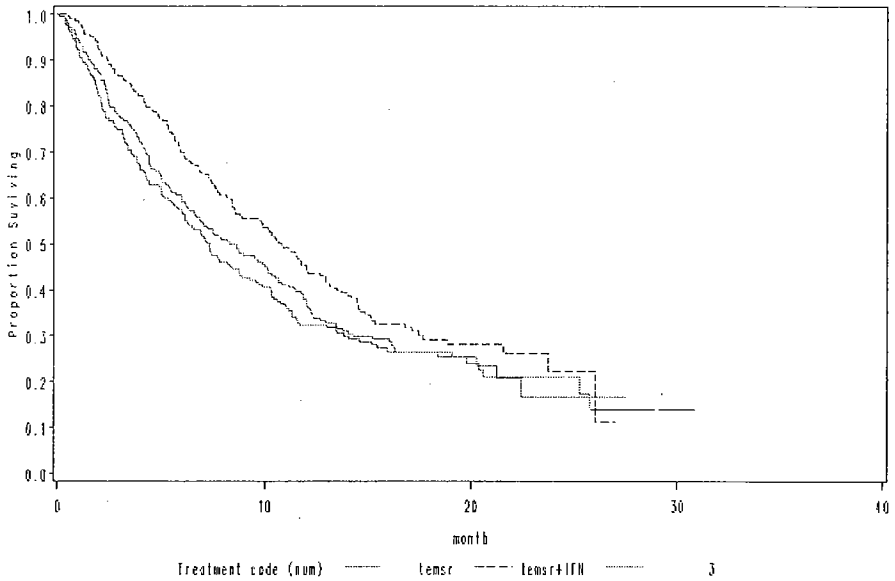
The Applicant performed an exploratory analysis of OS in patients who received no additional anti-cancer therapy after discontinuation of study treatment. They found that 153 patients in the IFN-α arm and 129 patients in the temsirolimus arm did not receive subsequent therapy during follow-up. The hazard ratio was 0.74 (95% CI, 0.56-0.98) comparing the temsirolimus and IFN-α arms (very similar to the hazard ratio of 0.73 for the ITT population). The difference in survival curves was statistically significant (p-value=0.0324). This result was consistent with the OS findings in the ITT population.

Table 6.6: Frequency of Select Subsequent Therapy Per Treatment Group (Applicant Analysis)

Number of Patients Who Received Subsequent Therapy	Temsirolimus (n=209)	**IFN-α** (n=207)	Tem + **IFN-α** (n=210)
Interferon	48	15	18
IL2	11	13	5
Bevacizumab	12	10	6
Sorafenib	8	6	5
Sunitinib	2	2	6

Reviewer Comment: Many more patients in the temsirolimus arm went on to receive interferon after progression of disease. Interferon has been demonstrated to prolong overall survival in previous trials. The use of interferon as subsequent therapy may confound the overall survival analysis for the temsirolimus arm. Confounding of this result is less likely given the exploratory analysis of survival for patients who did not receive subsequent therapy during follow-up. The use of interferon as subsequent therapy would not confound the response rate or time to progression results of this study because these endpoints do not include the time of subsequent therapy in the analysis. The use of other anticancer therapies during follow-up was similar across treatment groups and included IL-2, sunitinib, sorafenib, bevacizumab, gemcitabine, and vinblastine.

Figure 6.3: Kaplan-Meier Plot for Overall Survival in the ITT



(Biostatistician Figure)

Table 6.7: Overall Survival in ITT Population (FDA Analysis)

	IFN-α (n=207)	TEMSR (n=209)	IFN-α/TEMSR (n=210)
No. deaths (n, %)	149 (72.0)	143 (68.4)	154 (73.3)
Median OS in months (95% CI)	7.3 (6.1, 8.8)	10.9 (8.6, 12.7)	8.4 (6.6, 10.3)
% Change in Median OS from IFN-α	--	49%	15%
Hazard ratio (95% CI) log-rank p-value	--	0.73 (0.58, 0.92) 0.0078	0.96 (0.76, 1.20) 0.6965

Reviewer Comment: The results of this analysis of temsirolimus versus interferon demonstrate a substantial and clinically relevant improvement in overall survival. No significant confounding variables were identified. The Applicant analysis of overall survival was confirmed by the FDA data analysis using raw and derived datasets.

Subgroup Analyses

Subgroup analyses were undertaken with regard to the impact of nephrectomy status and region on OS evaluations. The results of the subgroup analyses of OS by stratification variables were consistent with the results in the ITT population. Overall, the analyses of OS and PFS by age, sex, and race were also consistent with the results for the ITT population.

A subgroup analysis was performed to evaluate whether the use of insulin impacted upon patient survival or progression-free survival. This analysis was undertaken because of concerns raised by Dr. Saber (Pharmacology Toxicology reviewer) that the use of insulin (being downstream from mTOR) might affect the efficacy of TORISEL. The results of these analyses can be found in table 6.8 below. Though this analysis does not take into account the significance of the patients' hyperglycemia or whether or not they were on insulin pre-trial, the subgroup analysis did not confirm this suspicion. The subset of patients who received insulin therapy during the trial appeared to have a longer median overall survival (15.1 months) than the ITT population (10.9 months). In a similar pattern, the subset of patients on the IFN-α/temsirolimus arm experienced a prolonged median OS (11.2 months) when insulin was concomitantly used compared to the ITT population OS of 8.4 months. These findings may possibly be explained by the patients with more m-TOR inhibition (and anticancer effect) causing more downstream effects, such as hyperglycemia. In addition, because this was an unplanned subgroup analysis, the results cannot be fully relied upon.

Table 6.8 Effect of Insulin Usage on Overall Survival

Effect of Insulin Use on Survival Endpoints	TEMSR With Insulin Use	TEMSR No Insulin Use	IFN-α\TEMSR With Insulin Use	IFN-α\TEMSR No Insulin Use
Dose	25 mg	25 mg	15 mg	15 mg
	(n=98)	(n=187)	(n=66)	(n=189)
Median OS in months (95% CI)	15.1 (15.1, 18.9)	10.9 (8.6, 12.7)	11.2 (9.9, 12.7)	8.8 (6.9, 10.9)
Hazard Ratio (95% CI)	1.488 (1.1, 2.0)		1.235 (0.87, 1.76)	
P-value	0.0106		0.2408	
Median PFS in months (95% CI)	7.9 (7.4, 9.2)	5.5 (3.9, 7.0)	7.4 (6.9,9.1)	5.0 (4.1, 6.0)
Hazard ratio (95% CI)	1.179 (0.9, 1.5)		1.46 (1.0, 2.0)	
Stratified log-rank P-value	0.2236		0.0221	

Response Rate

Response rate analyses were performed by this reviewer using the original submission raw TUMOR datasets numbered 1-5. This reviewer was unable to replicate the Applicant's results initially due to missing parts of electronic datasets.

Also noted during the review of the raw datasets was that the Applicant had not followed the pre-specified protocol with regard to the response analysis. Bone lesions were not measured using

MRI in all cases as planned (in patients who were enrolled with bone-only disease) and had measured bone lesions (mostly by CT) in patients who had soft tissue disease that met RECIST criteria. These protocol violations were communicated to the Applicant. The FDA review team requested that the Applicant reanalyze tumor response data according to protocol. This required the recalculation of PFS, ORR, and DOR endpoints. The reanalysis of ORR and PFS after submission of complete datasets was considered as a major amendment resulted in the extension of the PDUFA date. Upon reanalysis using the agreed upon techniques, the Applicant analysis was only changed by 0.2 months of PFS in patients in the IFN-α/temsirolimus arm. No changes in primary or secondary endpoints occurred in either the temsirolimus or IFN-α arm.

The biostatistical reviewer (Shan Sun-Mitchell, PhD) confirmed the Applicant's analyses using the derived data. No complete responses were seen in the independent radiologist reviewer findings. The Applicant described Stable Disease for at least 24 weeks as part of a combined endpoint of "Clinical Benefit Rate". Stable disease is not typically considered as strong evidence of clinical benefit. Therefore, it will not be discussed further in this review. The difference in response rates seen between the arms did not achieve statistical significance.

The response rate was slightly higher in the temsirolimus alone arm than in the combination arm. This is most likely explained by the inability to administer the intended dose intensity of the combination arm due to additive toxicities.

Table 6.9: Response Analysis (Applicant Independent Radiology Reviewer)

	Temsirolimus (n=209)	IFN-α (n=207)	Tem + IFN-α (n=210)
Partial Response Rate (95% CI; p-value)	8.6% (4.8, 12.4; 0.1232)	4.8% (1.9, 7.8)	8.1% (4.4, 11.8; 0.1822)
Complete Response Rate	0	0	0
P-value	0.7460	--	0.2143

Reviewer Comment: The improvement in response rate demonstrated with temsirolimus versus interferon- α was not statistically significant. This ORR analysis is not supportive of the overall efficacy evaluation. It is hypothesized that the response rate in the temsirolimus monotherapy arm was similar to that of the temsirolimus + interferon arm because both arms contained temsirolimus, which is active in this tumor.

Duration of Response

The Duration of Response was calculated from the date of first objective response to date of progression.

Table 6.10: Median Duration of Objective Response in ITT Population (Applicant Independent Radiology Reviewer)

	Temsirolimus (n=209)	IFN-α (n=207)	Tem + IFN-α (n=210)
Median Response Duration in Months	11.1	7.4	9.1
95% Confidence Interval	9.1, 13.8	3.9, 11.1	5.2, 13.6

Reviewer Comment: The difference in the median duration of response between arms did not achieve statistical significance. The duration of response cannot truly be compared because the statistic it is based upon did not achieve statistical significance. Also, this is a responder only analysis and not the ITT population. The duration of response endpoint cannot be supportive of the efficacy of temsirolimus in advanced RCC.

Progression Free Survival

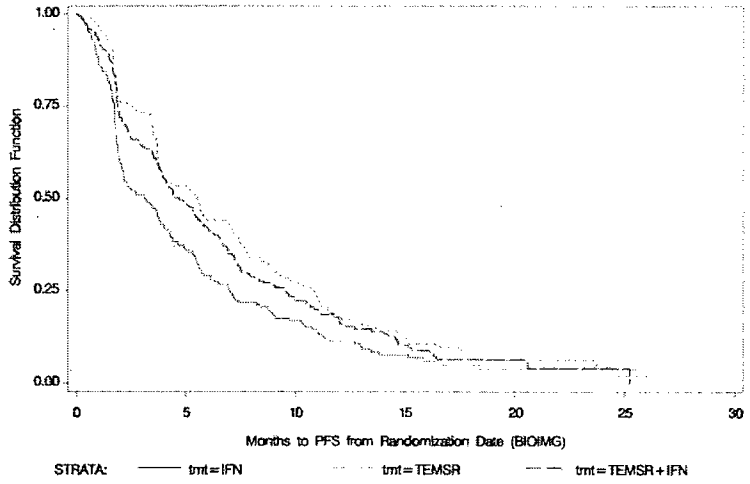
Progression Free Survival (PFS) was defined as the interval from the date of randomization until the earlier date of progression or death, censored at the last tumor evaluation date. Table 6.11 represents reanalysis of tumor response data used to support the secondary endpoints for the trial. This request was made because it was apparent to this reviewer that tumor measurements were not performed according to the protocol. The reviewer analysis of the amended data matched the Applicant analysis.

Table 6.11: Median PFS (Reviewer Table)

PFS in ITT Population by Independent Radiology Assessment			
	Temsirolimus (n=209)	**IFN-α (n=207)**	**Tem + IFN-α (n=210)**
Median PFS in mos (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	4.7 (3.9, 5.8)
Stratified log-rank p-value	0.0001*	--	0.0043*
Hazard Ratio	0.66 (0.53, 0.81)		0.73 (0.59, 0.90)

* P-values not adjusted for multiple comparisons

Figure 6.4: Kaplan-Meier Curve for PFS in ITT Population (Applicant Figure based upon Independent Radiologist Assessment)



Reviewer Comment: This analysis was reproduced and confirmed using raw data by this reviewer. The biostatistical reviewer (Shan Sun-Mitchell, PhD) confirmed the Applicant's analyses by the derived data. An improvement in PFS in the Torisel 25 mg arm was seen. These results demonstrate a clinically important improvement for these patients either by delaying onset of symptoms from recurrence or progression, or by delaying time to next potentially toxic treatment.

Subgroup Analyses

Subgroup analyses were undertaken with regard to the impact of nephrectomy status and region on PFS evaluations. Overall, the results of subgroup analyses of PFS by stratification variables were consistent with the results in the ITT population. Table 6.12, by Dr. Sun-Mitchell (Biostatistician) demonstrates the results of these analyses.

Table 6.12: Subgroup Analyses of Overall Survival in Stratification Factors

	IFN (n= 207)		TEMSR 25 mg (n= 209)				TEMSR 15 mg/IFN (n=210)			
		Median OS in months		**Median OS in months**	Hazard ratio	**P-value**	**n (%)**	**Median OS in months**	**Hazard ratio**	
Variable	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**	**(95 % CI)**			**(95% CI)**	**(95% CI)**	**P-value**
Prior nephrectomy						0.2037				0.3297
No	68 (32.9)	6.2 (3.8, 8.8)	70 (33.5)	11.5 (8.5, 14.5)	0.61 (0.41,0.91)		69 (32.9)	5.7 (3.4, 8.8)	1.09 (0.75, 1.59)	
Yes	139 (67.1)	7.8 (6.2, 10.6)	139 (66.5)	10.4 (8.2,13.0)	0.84 (0.63,1.11)		141 (67.1)	10.2 (7.3, 12.2)	0.86 (0.65,1.14)	
Region										
						0.8241				0.2313
Region 1	61(29.5)	70 (4.4,10.4)	61 (29.2)	10.4 (6.9, 13.0)	0.79 (0.52,1.21)		62 (29.5)	6.2 (4.3, 12.2)	0.94 (0.61,1.44)	
Region 2	43 (20.8)	6.3 (5.0, 8.8)	44 (21.1)	8.6 (6.4, 11.5)	0.81 (0.49,1.32)		42 (20.0)	5.1 (2.9, 9.0)	1.34 (0.83,2.15)	
Region 3	103(49.8)	7.8 (5.6,11.0)	104 (49.8)	12.9 (8.9, 14.5)	0.70 (0.51,0.98)		106 (50.5)	10.3 (7.5, 13.5)	0.84 (0.61,1.15)	

Reviewer Comments: Survival endpoints (OS and PFS) were not influenced by whether or not a patient had undergone nephrectomy or by region. The subgroup analyses of OS and PFS by the stratification variables of nephrectomy status and region were consistent with the results in the Intent To Treat (ITT) population. These analyses were not statistically significant and showed no evidence for a difference between the relative efficacy of temsirolimus with respect to nephrectomy status or region.

Time to Treatment Failure

As previously discussed in section 6.1.2, TTF is a composite endpoint of efficacy and safety. TTF analysis was not repeated by this reviewer because it is not considered clinically relevant [redacted] The statistical significance of the results of this analysis cannot be determined because the previous secondary endpoint (Response Rate) failed to achieve significance, thus using the remaining alpha.

Health Outcomes

Quality adjusted survival was compared, by the Applicant, across treatment groups. Their analysis found a statistically significant increase in quality adjusted survival (Q-TWiST) time of an estimated 1.3 months (7.0 vs. 5.7 months) in the Temsirolimus group as compared to interferon. This endpoint is a composite endpoint of toxicity and efficacy. No adjustment for multiple comparisons was performed for the safety endpoint analyses. This analysis was replicated by Dr. Sun-Mitchell using derived datasets. The statistical significance of the results of this analysis cannot be determined because the previous secondary endpoint (Response Rate) failed to achieve significance, thus using the remaining alpha.

[redacted]

Subject and caregiver reported outcomes

The Applicant performed an analysis of subject and caregiver reported outcomes. No prospective plan for the analysis of this data was revealed in the submitted statistical analysis plan. This analysis is not requested for inclusion in the label.

The phase 3, randomized, controlled trial is considered as having provided substantial evidence of the effectiveness of temsirolimus in advanced RCC. The study was well-controlled and

conducted by well-qualified experts in the field of oncology internationally. This study meets the criteria described in CRF 21 section 505(d).

6.1.5 Clinical Microbiology

N/A to an oncology drug.

6.1.6 Efficacy Conclusions

The trial provides substantial evidence of efficacy with results that are generalizable to a broad, international population of patients with advanced RCC. The trial used a comparator that can be considered the standard of care in the disease being studied and was conducted per protocol except for the response assessments, as discussed in section 6.1.4. The trial appears to have been well-conducted. The largest accruing groups were not found to have potentially confounding deficiencies on FDA site inspection. The endpoints of overall survival and objective response, when assessed by an independent radiology review team, are not subject to bias. The objective response analysis (using per protocol RECIST-based criteria) was repeated at the request of the review team.

Overall Strengths of Trial

- Well-designed, well-conducted, large, international trial
- Randomized to study drug, standard of care active control, or combination of both
- Powered for overall survival analysis which demonstrated advantage of study drug
- Independent radiological review limited potential for bias in response assessment

Overall Weaknesses of Trial

- Bone lesions permitted by protocol amendment (in patients with bone only disease) were not measured using pre-specified imaging technique (MRI)
- Bone lesions were measured and used as target lesions in patients who had measurable soft-tissue disease.

Summary of Efficacy Conclusions

- The results of the trial provide substantial evidence of efficacy of temsirolimus as a single agent in advanced renal cell carcinoma.

- A statistically significant overall survival advantage was demonstrated in patients who were randomized to the temsirolimus arm versus those who were randomized to the interferon-α arm. An overall survival trend was demonstrated in patients who were randomized to the temsirolimus + interferon-α group, but this difference was not statistically significant.

- An improvement in median progression free survival (unadjusted for multiple comparisons) was demonstrated in patients who were randomized to either temsirolimus-containing group vs. interferon-α.

- Overall response rate was numerically higher in patients treated with temsirolimus alone vs. interferon alfa, but did not reach statistical significance.

- The Q-TWiST analysis could not be supportive of clinical benefit due to multiple limitations in the way that the tool was used and inequality in missing data between arms.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

According to the applicant, a total of 1,080 individuals who have received IV temsirolimus form the basis of the original safety database for this NDA. This includes 416 subjects in the randomized phase III trial in advanced RCC, 179 subjects in phase I and phase II studies of advanced RCC, 178 subjects in three studies of other cancers (breast, prostate, and mantle cell lymphoma), 215 subjects in seven phase I studies in advanced solid tumors, and 92 healthy subjects in five phase I studies. Information on adverse events (AEs) is available until the data lock date of 05/30/2006 in the sponsor's original NDA submission.

In the randomized phase III trial of temsirolimus in advanced renal cell carcinoma (3066K1-304-WW), a clinical examination and measurement of coagulation parameters were performed at least every 4 weeks during treatment. A fasting chemistry panel was performed every 2 weeks, and a complete blood count (CBC) was performed weekly. After patients had been treated for 16 weeks, investigators were permitted to decrease the frequency of CBC to every 2 weeks and the frequency of chemistry panels to every 4 weeks if clinically appropriate. Investigators were directed to report as adverse events any laboratory abnormalities that were deemed clinically significant, with particular attention to grade 3 or 4 laboratory abnormalities. Electrocardiograms (ECGs) were performed at the screening visit and at the time of study withdrawal for all patients, and at two additional visits (first treatment and at three months) for a subset of patients enrolled in US and Canadian sites. A quality of life assessment tool (Euroqol EQ-5D) was administered weekly during treatment, and patients had weekly clinic visits at which they were encouraged to report adverse events. Adverse events were recorded in the case report form (CRF) with NCI toxicity grade, dates of onset and resolution, attribution of relationship to test article, outcome, and specific laboratory values where relevant.

This reviewer does not believe that the various studies can be pooled for the safety analysis because of the wide range of temsirolimus doses used, varied patient populations, and lack of appropriate controls, particularly given the high background rate of adverse events in patients

with advanced RCC. The results from Study 3066K1-304-WW, the randomized phase III trial in first-line treatment of advanced RCC, form the foundation of the safety analysis with use of the remainder of the safety database for assessment of serious and rare AEs.

Virtually all patients in every treatment arm of Study 3066K1-304-WW experienced at least one treatment-emergent adverse event (TEAE), and almost half of the patients had at least one serious adverse event (SAE). Single-agent temsirolimus was associated with a lower overall incidence of grade 3 and 4 TEAEs and SAEs than interferon or the combination. The incidence of TEAEs leading to treatment discontinuation and dose reduction was also lowest in the temsirolimus alone arm, although the temsirolimus alone arm had a higher incidence of TEAEs leading to dose delays.

Among patients receiving temsirolimus alone, the most common non-laboratory-related TEAEs (incidence ≥ 30%) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, hypocalcemia, elevated AST, and neutropenia. The most common grade 3 or 4 non-laboratory-related TEAEs (≥ 5% of patients) reported in patients receiving temsirolimus alone were: asthenia (11%), dyspnea (9%), rash (5%), and pain (5%).

In Study 3066K1-304-WW, abnormalities in laboratory parameters were common at baseline and while on treatment in all arms. The overall incidence of any grade of laboratory abnormalities on treatment was similar and approached 100% in all arms (TEMSR 100%, IFN-α/TEMSR 99%, IFN-α 97.5%). The overall incidence of grade 3 and 4 laboratory abnormalities on treatment was higher in the temsirolimus-containing arms (TEMSR 78%, IFN-α/TEMSR 83%) than in the interferon alone arm (72%).

The most common (≥40%) clinically important laboratory abnormalities in the temsirolimus arm were: decreased hemoglobin (94%), increased glucose (89%), increased cholesterol (87%), increased triglycerides (83%), decreased lymphocytes (72%), increased alkaline phosphatase (68%), increased creatinine (57%), decreased phosphorus (48%), and decreased platelets (40%). The most frequently reported (≥10%) grade 3/4 laboratory abnormalities in the temsirolimus arm were: increased triglycerides (44%), decreased hemoglobin (20%), decreased phosphorus (18%), increased glucose (16%), and decreased lymphocytes (16%).

A phase I study in healthy subjects to assess the effect of temsirolimus on QT/QTc interval was initiated shortly before the data lock date of 05/30/2006 and is ongoing, and data from the study have not yet been provided by the sponsor at the time of this review. A hepatic impairment study is also ongoing.

7.1.1 Deaths

There were 453 deaths reported in the ITT population of 3066K1-304-WW by the data lock date of 05/30/2006. The percentage of deaths was lowest in the temsirolimus alone arm (147/209,

70.3%) and similar in the IFN-α alone (152/207, 73.4%) and combination temsirolimus/ IFN-α (154/210, 73.3%) arms. According to the sponsor, approximately 91% of deaths (412/453) were due to disease progression.

Reviewer Comment: Deaths in the first 30 days on study occurred less often in the temsirolimus arm (2%) compared with the IFN-α alone arm (9%). Deaths within 30 days of last dose of study drug were slightly more common in the temsirolimus arm (11%) than in the IFN-α arm (9%). The majority of these deaths were due to disease progression.

In the safety population, there were 4 deaths in the temsirolimus alone arm compared with 18 in the IFN-α alone arm and 13 in the combination temsirolimus/ IFN-α arm within 30 days of first study drug administration. According to the sponsor's assessment, all 4 of the deaths in the first 30 days of treatment in the temsirolimus alone arm were a result of disease progression.

Table 7.1 Summary of Deaths in Study 3066K1-304-WW (ITT Population) from Sponsor

	IFN (n=207)	TEMSR 25 mg (n=209)	TEMSR 15 mg/IFN (n=210)	Total (n=626)
No. all deaths, n (%)	152 (73.4)	147 (70.3)	154 (73.3)	453 (72.4)
No. deaths among patients who did not receive test article, n (%)	4 (1.9)	1 (0.5)	2 (1.0)	7 (1.1)
No. deaths within 15 days of last dose, n (%)	24 (11.6)	13 (6.2)	30 (14.3)	67 (10.7)
No. deaths after 15 days from last dose, n (%)	124 (59.9)	133 (63.6)	122 (58.1)	379 (60.5)
Reason for death (n=453)[a]				
AE related to test article	1 (0.7)	2 (1.4)	7 (4.5)	10 (2.2)
Disease progression	136 (89.5)	139 (94.6)	137 (89.0)	412 (90.9)
Reason not specified	0	0	1 (0.6)	1 (0.2)
Other	15 (9.9)	6 (4.1)	9 (5.8)	30 (6.6)

Abbreviations: AE = adverse event; IFN = interferon-α; ITT = intent-to-treat; TEMSR = temsirolimus.
a. Percentages are based on number of patients who died in each treatment group.
Source: DTH4_ITT - 12JUN06 07:57.

Table 7.2 Deaths in First Thirty Days of Study Treatment by Regimen (Safety Population)

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days To Death	Cause of Death
TEMSR					
513001	**06/29/2004**	**07/05/2004**			**Disease Progression (Renal failure)**
806001	01/30/2004	02/06/2004			Disease Progression
068006	02/24/2005	03/10/2005			Disease Progression

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days To Death	Cause of Death
571002	08/23/2004	08/30/2004			Disease Progression
IFN					
311002	02/25/2004	03/03/2004			Disease Progression
505008	07/08/2004	07/12/2004			Disease Progression
046001	12/08/2003	12/16/2003			Disease Progression
525011	07/06/2004	07/10/2004			Disease Progression
029003	03/15/2004	03/17/2004			Other (Pulmonary Embolism)
517002	04/19/2004	04/28/2004			Disease Progression
523008	09/30/2004	10/14/2004			AE Related to Test Article (Cerebral vascular disorder)
531001	02/09/2004	02/13/2004			Disease Progression
811005	08/18/2004	09/01/2004			Other (Acute renal failure)
525012	10/13/2004	10/31/2004			Disease progression
508015	08/16/2004	09/03/2004			Disease Progression
530012	10/22/2004	11/05/2004			Disease progression
024001	10/15/2003	11/02/2003			Disease Progression
808001	05/18/2004	06/05/2004			Disease Progression
505004	02/06/2004	02/22/2004			Disease progression
052001	01/19/2004	02/09/2004			Disease Progression
542001	11/12/2004	11/24/2004			Disease Progression
018007	01/13/2005	02/06/2005			Other (Respiratory complication of COPD)
IFN/TEMSR					
027001	10/08/2003	10/08/2003			Other (Cardiac arrest)
562005	06/01/2004	06/05/2004			Disease Progression
312003	07/13/2004	07/21/2004			Disease Progression
535007	02/17/2005	03/01/2005			Disease progression
019002	05/12/2004	05/26/2004			Disease Progression
070003	**03/11/2004**	**03/19/2004**			**AE Related to test article (Renal failure)**
503007	03/14/2005	04/02/2005			Disease Progression
575001	**08/06/2004**	**08/19/2004**			**AE Related to Test Article (Bronchiolitis obliterans)**
036004	02/02/2005	02/21/2005			Disease Progression
553001	06/18/2004	06/29/2004			Disease Progression
573003	**09/06/2004**	**09/24/2004**			**Other (Brain hemorrhage,**

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days To Death	Cause of Death
			[redacted]		**probably cerebral stroke caused by arterial hypertension)**
029002	03/09/2004	03/25/2004			Disease Progression
062001	12/08/2004	12/29/2004			Disease progression

Datasets: DEATH.xpt and DEMOWIDE.xpt

Case report forms (CRFs) and sponsor comments have been reviewed for all patients receiving temsirolimus, either alone or in combination with interferon, who died within 30 days of beginning treatment and whose death was not due to disease progression alone. The narratives below have been compiled by this reviewer for patients whose deaths may have been due to an AE related to test article(s) either in the judgment of the investigator or this reviewer. The corresponding patients appear in bold in the table above.

Patient 513001 (Temsirolimus 25 mg IV 1x/wk): Disease Progression/Renal failure
Prior to starting treatment, this 72 year old woman had been hospitalized from [redacted] with pleural effusion, nonspecific ST depression, and an elevated international normalized ratio of prothrombin time (INR) for which she received IV vitamin K. Her creatinine during that hospitalization was 1.3 mg/dL. She received dose #1 of temsirolimus on 06/29/2004 and dose #2 on 07/05/2004. After dose #2, she developed progressive grade 3 somnolence with depressed level of consciousness and myositis. She was hospitalized on [redacted] with hyperuricemia and oliguric renal failure. She was treated with IV rehydration and oral allopurinol. She died 14 hours after hospital admission on [redacted] Per the CRF narrative: "The investigator stated that the cause of death was metabolic unbalance because of renal failure and the renal artery obstruction was caused by rapidly progressive disease (enlarged lymph nodes), but progressive disease was never confirmed radiologically." The investigator assessed the renal failure as probably not related to test article.

Patient 070003 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Renal failure
This 48 year old woman with a past medical history of hypertension, hypercholesterolemia, hypercalcemia, and a baseline creatinine of 1.6 mg/dL began treatment with IFN-α on 03/11/2004 and with temsirolimus on 03/18/2004. On [redacted] she was admitted with hemorrhage from the nose, mouth, and rectum (with a normal to elevated platelet count) and required 2 units of packed red blood cells and 6 units of fresh frozen plasma before the hemorrhage ultimately resolved on 03/21/2004. During the same period, she developed acute renal failure that required hemodialysis from 03/20/2004 to 03/26/2004. An abdominal ultrasound showed that her liver metastases were larger, and chest x-rays indicated possible fluid overload and/or pulmonary edema. She died of acute renal failure on [redacted]. The investigator ruled the hemorrhage as possibly related and the renal failure as probably related to test article.

Patient 575001 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Bronchiolitis obliterans

This 69 year old man with stage IV RCC had received 2 prior courses of radiotherapy to the lumbosacral spine (8 Gy on 07/20/2004) and to the mediastinum and right lung (16 Gy from 07/20-07/21/2004). He began IFN-α on 08/06/2004 and received his first and only dose of temsirolimus on [redacted] About 24 hours after the temsirolimus dose was administered, he experienced acute onset of dyspnea requiring hospitalization and treatment with oxygen, furosemide, IV antibiotics, and IV dexamethasone. He was withdrawn from the treatment phase of the study due to this AE on 08/20/2004 and after a temporary improvement in his respiratory status with an increased dose of dexamethasone, his condition worsened again and he died on [redacted] A limited autopsy performed on [redacted] showed in the lungs "signs of fulminant (retro-obstructive) bronchopneumonia, focal signs of cavitations, and necrosis" and "the spleen had a pulp consistency (probably due to sepsis)." The family denied consent for microscopic postmortem examination. The cause of death was reported as bronchiolitis obliterans probably related to test article per the investigator.

Patient 573003 (Temsirolimus 15 mg IV 1x/wk and IFU 6 MU SQ 3x/wk): Cerebral hemorrhage

This 66 year old man with a past medical history of mild hypertension and hydrocephalus, but no brain metastases on imaging in 08/2004, began IFN-α on 09/02/2004 and temsirolimus on 09/10/2004. On 09/24/2004 (week 3), he received temsirolimus in the morning and IFN-α in the evening. He had no AEs reported during treatment and a blood pressure of 150/90 mm Hg. On 09/25/2004, he experienced a severe headache over 14 hours and ultimately a left-sided hemiplegia. He was withdrawn from treatment on 09/28/2004 due to AE termed a "hemorrhagic brain insult," though no imaging was ever performed because the patient was not taken to the hospital. He went into a coma on [redacted] and remained so until he died at home on [redacted] No autopsy was performed. The death was termed a hemorrhagic brain insult leading to death probably not related to test article per the investigator.

In the safety population, there were 23 deaths in the temsirolimus alone arm compared with 18 in the IFN-α alone arm and 26 in the combination temsirolimus/ IFN-α arm after the first 30 days of treatment and within 30 days of last study drug administration. According to the sponsor's assessment, deaths due to disease progression were similar in the temsirolimus alone (74%) and IFN-α alone (73%) arms. There were 2 deaths attributed to test-article related AEs in the temsirolimus arm and none in the IFN-α arm.

Table 7.3 Deaths Within 30 Days of Last Treatment and After First 30 Days of Treatment (Safety Population)

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days to Death	Cause of Death
TEMSR					
020004	**12/08/2004**	**02/01/2005**	[redacted]		**AE Related to Test**

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days to Death	Cause of Death
					Article (Hyperkalemia)
024006	03/14/2005	05/09/2005			Disease Progression
524006	**05/14/2004**	**07/02/2004**			**Other (Stroke)**
304001	**03/04/2004**	**02/08/2005**			**Other (Congestive heart failure)**
503001	05/11/2004	06/08/2004			Disease Progression
801003	08/31/2004	12/07/2004			Disease Progression
037003	07/27/2004	08/24/2004			Disease Progression
037003	07/27/2004	08/24/2004			Disease Progression
068006	02/24/2005	03/10/2005			Disease Progression
525006	04/20/2004	06/03/2004			Disease Progression
574003	09/13/2004	03/23/2005			Other (Possible pulmonary embolism)
505002	02/06/2004	03/24/2004			Disease Progression
016019	**12/02/2004**	**03/10/2005**			**Disease progression causing bowel perforation**
535003	09/14/2004	03/08/2005			Disease Progression
006003	11/12/2004	11/26/2004			Disease Progression
022001	03/18/2004	04/15/2004			Disease Progression
057002	10/03/2003	10/24/2003			Disease Progression
500015	02/28/2005	04/18/2005			Disease Progression
530013	**11/10/2004**	**11/17/2004**			**AE Related to Test Article (Acute renal failure)**
535006	01/31/2005	03/21/2005			Disease progression
813006	11/25/2004	03/17/2005			Disease Progression
821002	03/15/2005	01/30/2006			Other: AE unrelated to test article (Pneumonia and hypercalcemia)
510004	04/21/2004	05/31/2004			Disease Progression (Pulmonary edema)
IFN					
573005	12/01/2004	06/10/2005			Other (Acute cardiac insufficiency)
513002	06/28/2004	08/25/2004			Disease Progression
535008	02/08/2005	03/28/2005			Disease Progression
801005	02/15/2005	03/21/2005			Disease Progression
528002	12/22/2003	01/12/2004			Disease Progression
571003	08/30/2004	10/22/2004			Disease Progression
001002	10/13/2003	11/24/2003			Disease Progression

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days to Death	Cause of Death
565001	06/15/2004	07/20/2004			Disease Progression
502009	03/04/2005	08/09/2005			Other (Symptomatic deterioration)
018004	09/22/2004	02/21/2005			Other (COPD, acute myocardial infarction)
806003	05/03/2004	05/28/2004			Disease Progression
550001	05/21/2004	06/23/2004			Disease Progression
596007	09/27/2004	10/29/2004			Other (Multi-organ failure)
518002	03/22/2004	05/10/2004			Disease progression
016003	02/05/2004	02/17/2004			Other (Cardiopulmonary collapse)
562004	05/17/2004	07/12/2004			Disease Progression
562008	07/16/2004	01/31/2005			Disease Progression
550003	06/08/2004	07/04/2004			Disease Progression
IFN/TEMSR					
541003	12/06/2004	02/08/2005			Other: (Pneumonia)
050004	07/14/2004	07/18/2005			Disease Progression
523002	12/27/2003	01/29/2004			Disease Progression
600001	**10/21/2004**	**11/21/2004**			**AE Related to Test Article (Acute myocardial infarction, acute renal failure)**
508024	**11/03/2004**	**05/21/2005**			**AE Related to Test Article (Cerebral stroke)**
562001	04/28/2004	06/14/2004			Disease Progression
506004	**12/11/2003**	**02/15/2004**			**AE Related to Test Article (Acute renal failure)**
508009	05/10/2004	08/21/2004			Disease Progression
528001	12/01/2003	12/31/2003			Disease progression
541005	12/20/2004	01/26/2005			Disease Progression
008005	**12/13/2004**	**01/17/2005**			**AE Related to Test Article (Acute renal failure, Adult Respiratory Distress Syndrome)**
530009	09/24/2004	12/04/2004			Disease Progression
821001	03/16/2005	09/14/2005			Disease Progression
304004	08/24/2004	03/25/2005			Disease Progression
508006	**03/26/2004**	**09/29/2004**			**AE Related to Test**

Patient ID	Treatment Start Date	Treatment Stop Date	Date of Death	Days to Death	Cause of Death
					Article (Heart failure and respiratory failure)
517001	04/14/2004	06/02/2004			Disease progression
588001	10/01/2004	11/27/2004			Other (Pneumonia due to bronchoaspiration)
037011	04/04/2005	05/14/2005			Disease Progression
801004	09/21/2004	12/31/2004			Disease Progression
521009	08/27/2004	10/20/2004			Disease Progression
528005	03/22/2004	04/19/2004			Disease Progression
040004	12/30/2003	04/12/2004			Disease Progression
523004	04/01/2004	05/18/2004			Disease Progression
570011	09/08/2004	11/09/2004			Disease Progression
806002	03/31/2004	05/24/2004			Disease Progression
579005	02/05/2004	02/26/2004			Disease Progression

Datasets: DEATH.xpt and DEMOWIDE.xpt

Case report forms and sponsor comments have been reviewed for all patients receiving temsirolimus, either alone or in combination with interferon, who died more than 30 days after beginning treatment and within 30 days of the last dose of treatment, whose death was not due solely to disease progression. The narratives below have been compiled by this reviewer for patients whose deaths may have due to an AE related to test article(s) either in the judgment of the investigator or this reviewer. The corresponding patients appear in bold in the table above.

Patient 020004 (Temsirolimus 25 mg IV 1x/wk arm): Hyperkalemia

This 61 year old female had a past medical history of hypertension and pulmonary embolus. She began temsirolimus 25 mg on 12/08/2004. She experienced anaphylactoid hypersensitivity with doses #1 and 2. Prior to subsequent doses, she was pre-treated with Decadron and received them without incident. During weeks 7/8 of treatment, her potassium and liver function tests were normal, her creatinine was 1.7 mg/dL, and her LDH was 989 U/L (upper limit of normal: 600 U/L). She received her ninth dose on [redacted] and was hospitalized the same day with electrolyte derangement following treatment (Na 125 mmol/L, K 6.2 mmol/L, BUN 45 mg/dL, Cre 2.2 mg/dL, Gluc 265 mg/dL, AST 119 U/L, ALT 104 U/L, LDH 1,718 U/L). The abnormalities were attributed to tumor necrosis and volume depletion. Despite treatment with IV fluids, sodium polystyrene sulfonate (Kayexalate), insulin, and glucose, her chemistries continued to worsen over the following day (Cre 3.3 mg/dL, AST 10,700 U/L, ALT 7,808 U/L, Tbili 4.5 mg/dL, Na 126 mmol/L, K 6.4 mmol/L, LDH 67,431 U/L). The hyperkalemia failed to respond to hemodialysis. She developed progressive widening of the QRS complex with arrhythmias and ultimately expired from pulseless electrical activity followed by asystole on [redacted] An autopsy reported the cause of death as "cardiac arrhythmia secondary to electrolyte abnormalities". The liver showed "recent necrosis of the centrilobular areas of the liver," a pattern most often due to ischemia. The autopsy also noted extensive tumor burden in

the right kidney, and multiple metastases in the liver, lungs, and retroperitoneal nodes. The investigator ruled her death possibly related to test article.

Patient 524006 (Temsirolimus 25 mg IV 1x/wk arm): Cerebrovascular accident
This 58 year old woman with no past medical history began treatment with Temsirolimus 25 mg IV on 05/14/2004. She suffered an acute cerebrovascular accident (CVA) in week [redacted] of treatment on [redacted] and died the same day in the hospital. No autopsy was performed. The investigator judged her death definitely not related to test article.

Patient 304001 (Temsirolimus 25 mg IV 1x/wk arm): Congestive heart failure
This 76 year old woman with a past medical history of hypertension began treatment with temsirolimus on 03/04/2004 and was treated with no dose interruptions or modifications until week 48 (01/25/2005). She was admitted [redacted] for dyspnea and was found to have bilateral pleural effusions and diagnosed with pneumonia. She was treated with IV moxifloxacin and received nitroglycerin and morphine for chest pain. Temsirolimus was held for one week, she recovered, and she was discharged on [redacted] On [redacted] she received her next scheduled dose of temsirolimus. The following day, she experienced the same symptoms and was again admitted and found to have "pneumonia and pleural effusion". She died on [redacted] with her cause of death reported as congestive heart failure resulting from pneumonia and pleural effusions. Her death was judged definitely not related to test article by the investigator.

Patient 016019 (Temsirolimus 25 mg IV 1x/wk arm): Bowel perforation
This 67 year old woman had a past medical history of breast cancer s/p bilateral mastectomy in 1976 and uterine cancer s/p hysterectomy and radiation to total dose of 4500 cGy in 1996. She began temsirolimus 25 mg on 12/02/2004 and received a total of 13 doses over 15 wks. She received her last dose on [redacted] and five days later had fever, nausea, hematemesis, abdominal pain, tachycardia and hypotension. A CT scan was reported to show "free air, ascites, and multiple new mets," and was interpreted as consistent with "peritonitis and bowel perforation" with either transverse color or adjuvant loop of small bowel as the suspected site of perforation. She was treated with IV ampicillin/sulbactam and a morphine PCA and was discharged to home hospice on [redacted] The discharge summary noted that the patient "reported having had diarrhea for more than a month and recent jelly red/black bowel movements." She died on [redacted] with cause of death reported to be "progressive disease". The investigator assessed her death as probably not related to test article.

Patient 530013 (Temsirolimus 25 mg IV 1x/wk arm): Renal failure
This 69 year old man with no past medical history and a baseline creatinine of 1.3 mg/dL began treatment with TEMSR on 11/10/2004. He received two weekly doses, but then experienced a number of grade 2 and 3 AEs, including anorexia, nausea, vomiting, and diarrhea, and his week 3 and 4 doses were withheld. He was hospitalized for grade 3 diarrhea and acute renal failure on [redacted] His diarrhea resolved on 12/3/2004, but the acute renal failure with hypernatremia and generalized edema persisted. He began to experience hypoxia on 12/6/04. He died on [redacted] with acute renal failure reported by the investigator as his immediate cause of death and judged possibly related to test article.

Patient 050004 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Cardiomyopathy and pulmonary infiltrates

This 46 year old male former smoker with no other relevant past medical history began treatment on 07/24/2004 with IFN-α and temsirolimus. He was admitted on [redacted] with dyspnea and hypoxemia of sudden onset, requiring intubation. A chest x-ray showed new pulmonary infiltrates, his troponin was elevated, and an ECG showed changes of unknown significance. His echocardiogram showed a global reduction in left ventricular function with an ejection fraction of 10-15% but no specific wall motion abnormalities. He received oxygen, antibiotics, and enoxaparin, but rapidly deteriorated. He died on [redacted] with his cause of death reported as cardiomyopathy and pulmonary infiltrates judged possibly related to test article. An autopsy was not performed.

Patient 600001 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Acute myocardial infarction and acute renal failure

This 59 year old man with no past medical history and a normal creatinine at baseline began IFN-α on 10/21/2004 and temsirolimus on 10/26/2004. He experienced a grade 2 increase in creatinine and fevers on 11/2/2004. He continued temsirolimus and IFN-α, with continuing elevation of his creatinine. His last dose of temsirolimus was 11/16/2004, and his last dose of IFN-α was 11/21/2004. On [redacted] he was hospitalized with life-threatening renal failure. The same day, he also experienced a grade 5 acute anterolateral myocardial infarction. He died on [redacted] of acute myocardial infarction and acute renal failure judged by the investigator to be possibly and probably related to test article, respectively.

Patient 508024 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Cerebral stroke

This 63 year old man with no relevant past medical history began treatment with IFN-α on 11/3/2004 and temsirolimus on 11/10/2004. His study course was notable for hypertension requiring treatment with enalapril, grade 3 thrombocytopenia, and anemia requiring blood transfusion and temporary discontinuations of IFN-α and temsirolimus. He was noted to have grade 3 mucositis at week 11 on 01/12/2005, so both study drugs were held for one week. He received full dose temsirolimus and IFN-α on 01/19/2005. He was hospitalized on [redacted] with fever, abdominal pain, and vomiting and was found to have an appendiceal perforation and peritonitis and was treated with appendectomy and IV antibiotics. This event was judged to be not related to test article, and the patient recovered. On [redacted] he was hospitalized in a moribund state and required intubation for apnea. He was noted to have a platelet count of 69,000. He died on [redacted] of a cerebrovascular accident (CVA) that was assumed to be hemorrhagic because of coexisting thrombocytopenia, hypertension, and rapid course. The CVA was judged possibly related to test article by the investigator.

Patient 506004 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Renal failure

This 59 year old man with a normal baseline creatinine and no past medical history began treatment with IFN-α and temsirolimus on 12/11/2003. His course was complicated by dehydration and anemia requiring hospitalization and blood transfusion on [redacted] His last dose of study medication was 02/15/2004. He was hospitalized again on [redacted] for

asthenia, mucosal bleeding with laboratory abnormalities consistent with disseminated intravascular coagulation, and acute renal failure. He became anuric and failed to respond to any treatment measures, and subsequently died on [redacted] of renal failure. No autopsy was performed. The renal failure was judged possibly related to test article by the investigator.

Patient 008005 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Renal failure
This 71 year old man with a past medical history of hypertension, chronic obstructive pulmonary disease, coronary artery disease, and a baseline creatinine of 1.7 mg/dL began treatment with IFN-α on 12/13/2004 and temsirolimus on 12/20/2004. Treatment was held for one week at week 3 due to thrombocytopenia. On 01/17/2005, his creatinine was elevated to 3.5 mg/dL, but dosing was continued. He presented to an emergency room on [redacted] for dizziness and feeling unwell and was admitted with a platelet count of 45,000 and a creatinine of 3.6 mg/dL. During that hospitalization, he developed adult respiratory distress syndrome (ARDS) for unclear reasons requiring mechanical ventilation. He died on [redacted] of acute renal failure and ARDS, both judged to be definitely related to test article(s) by the investigator.

Patient 508006 (Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SC 3x/wk): Heart failure and respiratory failure
This 60 year old man with a past medical history of hypertension, hyperlipidemia, and coronary artery disease began treatment with IFN-α on 03/26/2004 and temsirolimus on 04/02/2004. His treatment course was complicated by pneumonia, anemia requiring blood transfusion, hypocalcemia, and thrombocytopenia requiring multiple treatment interruptions and dose reductions. His last dose of study drug was on 09/29/2004. On 10/01/2004 (week 28), he presented with grade 4 anemia and ultimately grade 5 heart failure and respiratory failure. He died on [redacted] due to heart failure and respiratory failure judged definitely related to study drug by the investigator.

7.1.2 Other Serious Adverse Events

Other Serious Adverse Events
Definition of a Serious Adverse Event (SAE):
According to 21 CFR 312 (a), a serious adverse experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
"Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect."

"Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

Reviewer Comment: Deaths within 30 days of first drug administration and within 30 days of last drug administration have been discussed in the previous section. No pregnant women were allowed on the trial. While the sponsor provided overall SAE data/tables/analysis, including NCI CTC v3 toxicity grade, and an analysis of these SAEs in the clinical study report, the SAEs were not subdivided by category (e.g. disability/incapacity, life-threatening drug experience, etc) in the clinical database. Incorporation of these data, which are currently contained in the CRFs and the company's pharmacovigilance database, into the clinical datasets was possible but would have been a lengthy process that would make completing the review in a timely fashion very difficult. Furthermore, this medical team believes that analysis of grade 3 and 4 TEAEs provides a more meaningful assessment of SAEs in the advanced cancer population. In light of these points, SAE data subdivided by category of SAE were not required to be submitted by the sponsor. SAEs resulting in hospitalization and grade 3 and 4 TEAEs will be discussed below.

Hospitalizations:

A total of 3,154 hospitalizations occurred in the pivotal trial. These were least common in the IFN-α arm (n=803) and similar in the temsirolimus arm (n=1192) and the combination IFN-α/temsirolimus arm (n=1149).

Reviewer Comment: In this multinational study, reasons for hospitalization may differ from those in the USA. It may be more relevant to use the NCI CTC criteria to evaluate the severity of adverse events for approval of drugs in the USA.

AEs leading to hospitalization:

There were 715 SAEs resulting in hospitalization. Twenty-seven percent (n=192) of these occurred in the temsirolimus arm compared with 29% (n=205) in the IFN-α arm and 44% (n=318) in the combination IFN-α/temsirolimus arm. One hundred and seventy five of these reported SAEs resulting in hospitalization were grade 2 or less in severity. These also occurred least often in the temsirolimus alone arm (n=41) compared to the IFN-α (n=58) or IFN-α/ temsirolimus (n=76) arms. The most common grade 1 and 2 SAEs that led to hospitalization are in decreasing order of frequency: fever (n=15), anemia (n=9), pneumonia (n=8), pleural effusion (n=8), hypercalcemia (n=7), atrial fibrillation (n=7), confusion (n=6), peripheral edema (n=5), diarrhea (n=6), acute renal failure (n=5), and abdominal pain (n=5). Grade 3 and 4 TEAEs will be discussed in greater detail below.

Grade 3 or 4 Adverse Events

A total of 2,702 grade 3 and 4 treatment-emergent adverse events (TEAEs) were reported in Study 3066K1-304-WW. The overall incidence of grade 3 and 4 TEAEs was 14% lower in the

temsirolimus arm compared with the IFN-α arm. Sixty-nine percent (69%) of patients on the temsirolimus arm experienced at least one grade 3 or 4 TEAE compared with 78% of patients in the IFN-α arm and 87% of patients on the combination IFN-α/temsirolimus arm.

Reviewer Note: Among patients randomized to the temsirolimus arm, the body systems most often affected by grade 3 or 4 TEAEs were metabolic and nutritional (33%), body as a whole (27%), and hemic and lymphatic system (26%).

The most common grade 3 and 4 TEAEs in the temsirolimus arm were anemia (19.7%), hyperglycemia (10.6%), asthenia (10.1%), dyspnea (8.2%), hypophosphatemia (5.3%), rash (5.2%), pain (4.8%), abdominal pain (4.3%), lymphopenia (4.3%), and hypokalemia (3.4%).

Grade 3 and 4 TEAEs that occurred in at least 1% of patients on the temsirolimus arm and in at least twice as many patients as in the IFN-α arm included: hyperglycemia (10.6% versus 1.5%), hypophosphatemia (5.3% versus 0.5%), hypokalemia (3.4% versus 0%), hyperlipemia (2.9% versus 1%), peripheral edema (2.4% versus 0%), rash (2.5% versus 0%), stomatitis (1.4% versus 0%), diabetes mellitus (1.4% versus 0%), maculopapular rash (1.4% versus 0%), and pruritic rash (1.4% versus 0%).

Other grade 3 and 4 TEAEs that occurred in greater than 1% of patients in the temsirolimus arm included: back pain, accidental injury, infection, hypertension, anorexia, nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, increased creatinine, dehydration, increased alkaline phosphatase, hypercalcemia, peripheral edema, increased SGOT, weight loss, bone pain, somnolence, pleural effusion, pneumonia, and urinary tract infection.

Table 7.4 All Grade 3 and 4 Treatment Emergent Adverse Events (Safety Population)

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
GENERAL						
Local reaction to procedure	2	1.0	0	0.0	0	0.0
WHOLE BODY						
Asthenia	21	10.1	52	26.0	59	28.4
Pain	10	4.8	4	2.0	12	5.8
Abdominal pain	9	4.3	3	1.5	7	3.4
Back pain	6	2.9	7	3.5	4	1.9
Accidental injury	3	1.4	2	1.0	3	1.4
Infection	3	1.4	0	0.0	4	1.9
Chest pain	2	1.0	2	1.0	4	1.9
Malaise	2	1.0	1	0.5	0	0.0

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Abscess	1	0.5	0	0.0	0	0.0
Carcinoma	1	0.5	0	0.0	0	0.0
Cellulitis	1	0.5	1	0.5	3	1.4
Chills	1	0.5	3	1.5	1	0.5
Face edema	1	0.5	0	0.0	0	0.0
Fever	1	0.5	7	3.5	7	3.4
General physical health deterioration	1	0.5	1	0.5	1	0.5
Headache	1	0.5	0	0.0	0	0.0
Hernia	1	0.5	0	0.0	0	0.0
Non-specified drug reaction	1	0.5	0	0.0	0	0.0
Pelvic pain	1	0.5	0	0.0	0	0.0
Peritonitis	1	0.5	0	0.0	0	0.0
Sepsis	1	0.5	0	0.0	3	1.4
CARDIOVASCULAR SYSTEM						
Hypertension	3	1.4	0	0.0	1	0.5
Deep vein thrombosis	2	1.0	1	0.5	1	0.5
Heart failure	2	1.0	0	0.0	0	0.0
Atrial fibrillation	1	0.5	1	0.5	0	0.0
Cardiomyopathy	1	0.5	0	0.0	0	0.0
Congestive heart failure	1	0.5	0	0.0	1	0.5
Cyanosis	1	0.5	1	0.5	1	0.5
Intracranial hemorrhage	1	0.5	0	0.0	0	0.0
Myocardial infarct	1	0.5	1	0.5	0	0.0
Pericardial effusion	1	0.5	1	0.5	0	0.0
Peripheral gangrene	1	0.5	0	0.0	0	0.0
Pulmonary embolus	1	0.5	0	0.0	2	1.0
Syncope	1	0.5	1	0.5	1	0.5
Tachycardia sinus	1	0.5	0	0.0	0	0.0
DIGESTIVE SYSTEM						
Anorexia	6	2.9	8	4.0	16	7.7
Nausea	5	2.4	9	4.5	7	3.4
Vomiting	4	1.9	5	2.5	5	2.4
Diarrhea	3	1.4	4	2.0	11	5.3
Stomatitis	3	1.4	0	0.0	10	4.8
Gastrointestinal hemorrhage	2	1.0	0	0.0	0	0.0
Mucositis	2	1.0	0	0.0	11	5.3
Abdominal distension	1	0.5	0	0.0	0	0.0
Aphthous stomatitis	1	0.5	0	0.0	0	0.0

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Gamma glutamyl transpeptidase increased	1	0.5	2	1.0	2	1.0
Intestinal perforation	1	0.5	0	0.0	0	0.0
Periodontitis	1	0.5	0	0.0	1	0.5
Tongue edema	1	0.5	0	0.0	0	0.0
ENDOCRINE SYSTEM						
Diabetes mellitus	3	1.4	0	0.0	0	0.0
HEMIC AND LYMPHATIC SYSTEM						
Anemia	41	19.7	43	21.5	80	38.5
Lymphopenia	9	4.3	10	5.0	15	7.2
Neutropenia	6	2.9	14	7.0	32	15.4
Thrombocytopenia	3	1.4	0	0.0	18	8.7
Activated partial thromboplastin time prolonged	2	1.0	3	1.5	1	0.5
International normalised ratio increased	1	0.5	0	0.0	1	0.5
Leukopenia	1	0.5	10	5.0	18	8.7
Sedimentation rate increased	1	0.5	0	0.0	0	0.0
NUTRITIONAL AND METABOLIC						
Hyperglycemia	22	10.6	3	1.5	12	5.8
Hypophosphatemia	11	5.3	1	0.5	13	6.3
Hypokalemia	7	3.4	0	0.0	3	1.4
Creatinine increased	6	2.9	1	0.5	7	3.4
Hyperlipemia	6	2.9	2	1.0	16	7.7
Dehydration	5	2.4	8	4.0	11	5.3
Peripheral edema	5	2.4	0	0.0	0	0.0
Hypercalcemia	4	1.9	5	2.5	2	1.0
Alkaline phosphatase increased	3	1.4	8	4.0	11	5.3
SGOT increased	3	1.4	8	4.0	9	4.3
Weight loss	3	1.4	4	2.0	13	6.3
Bilirubinemia	2	1.0	3	1.5	0	0.0
Hyperkalemia	2	1.0	6	3.0	3	1.4
Hypocalcemia	2	1.0	7	3.5	7	3.4
Hypomagnesemia	2	1.0	1	0.5	3	1.4
Edema	1	0.5	1	0.5	1	0.5
Hypercholesteremia	1	0.5	0	0.0	4	1.9
Hyperuricemia	1	0.5	1	0.5	2	1.0
Hypoglycemia	1	0.5	0	0.0	2	1.0
Hyponatremia	1	0.5	2	1.0	8	3.8

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Hypoproteinemia	1	0.5	2	1.0	2	1.0
Lactic dehydrogenase increased	1	0.5	1	0.5	1	0.5
SGPT increased	1	0.5	4	2.0	2	1.0
Weight gain	1	0.5	2	1.0	0	0.0
MUSCULOSKELETAL						
Bone pain	3	1.4	3	1.5	3	1.4
Arthralgia	2	1.0	2	1.0	7	3.4
Pathological fracture	2	1.0	0	0.0	1	0.5
Myalgia	1	0.5	2	1.0	2	1.0
Spinal fracture	1	0.5	0	0.0	0	0.0
NERVOUS SYSTEM						
Somnolence	3	1.4	5	2.5	2	1.0
CNS depression	1	0.5	1	0.5	3	1.4
Dizziness	1	0.5	4	2.0	0	0.0
Hallucinations	1	0.5	1	0.5	1	0.5
Insomnia	1	0.5	0	0.0	4	1.9
Neuralgia	1	0.5	0	0.0	0	0.0
Neuropathy	1	0.5	2	1.0	2	1.0
Paresis	1	0.5	0	0.0	0	0.0
Paresthesia	1	0.5	0	0.0	0	0.0
Spinal cord compression	1	0.5	1	0.5	1	0.5
RESPIRATORY SYSTEM						
Dyspnea	17	8.2	10	5.0	19	9.1
Pleural effusion	5	2.4	3	1.5	1	0.5
Pneumonia	5	2.4	4	2.0	8	3.8
Asthma	2	1.0	1	0.5	1	0.5
Cough increased	2	1.0	0	0.0	4	1.9
Bronchitis	1	0.5	3	1.5	2	1.0
Carcinoma of lung	1	0.5	0	0.0	0	0.0
Hemothorax	1	0.5	0	0.0	0	0.0
Hypoxia	1	0.5	0	0.0	2	1.0
Pneumonitis	1	0.5	0	0.0	0	0.0
Pneumothorax	1	0.5	0	0.0	0	0.0
Respiratory failure	1	0.5	1	0.5	1	0.5
Wheezing	1	0.5	0	0.0	0	0.0
SKIN AND APPENDAGES						
Rash	5	2.4	0	0.0	2	1.0
Maculopapular rash	3	1.4	0	0.0	0	0.0

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Pruritic rash	3	1.4	0	0.0	0	0.0
Dry skin	1	0.5	0	0.0	0	0.0
Pruritus	1	0.5	0	0.0	0	0.0
Skin ulcer	1	0.5	0	0.0	0	0.0
Subcutaneous emphysema	1	0.5	0	0.0	0	0.0
Urticaria	1	0.5	0	0.0	1	0.5
SPECIAL SENSES						
Conjunctivitis	1	0.5	0	0.0	0	0.0
UROGENITAL						
Urinary tract infection	3	1.4	0	0.0	1	0.5
Acute kidney failure	2	1.0	3	1.5	1	0.5
Glomerulitis	1	0.5	0	0.0	0	0.0
Uremia	1	0.5	0	0.0	0	0.0
Urine abnormality	1	0.5	0	0.0	0	0.0

Datasets: ADVERSE.xpt + BASELINE.xpt
Reviewer note: Table above includes all grade 3 and 4 TEAEs in the Safety Population that occurred in at least one patient on the temsirolimus arm.

Table 7.5 Grade 3 and 4 Treatment-Emergent Adverse Events Observed in Greater Than 1% of Patients on the Temsirolimus Arm (Safety Population)

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
GENERAL						
Asthenia	21	10.1	52	26.0	59	28.4
Pain	10	4.8	4	2.0	12	5.8
Abdominal pain	9	4.3	3	1.5	7	3.4
Back pain	6	2.9	7	3.5	4	1.9
Accidental injury	3	1.4	2	1.0	3	1.4
Infection	3	1.4	0	0.0	4	1.9
CARDIOVASCULAR						
Hypertension	3	1.4	0	0.0	1	0.5
DIGESTIVE SYSTEM						
Anorexia	6	2.9	8	4.0	16	7.7
Nausea	5	2.4	9	4.5	7	3.4
Vomiting	4	1.9	5	2.5	5	2.4
Diarrhea	3	1.4	4	2.0	11	5.3

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Stomatitis	3	1.4	0	0.0	10	4.8
ENDOCRINE						
Diabetes mellitus	3	1.4	0	0.0	0	0.0
HEMIC/LYMPHATIC						
Anemia	41	19.7	43	21.5	80	38.5
Lymphopenia	9	4.3	10	5.0	15	7.2
Neutropenia	6	2.9	14	7.0	32	15.4
Thrombocytopenia	3	1.4	0	0.0	18	8.7
NUTRITIONAL/METABOLIC						
Hyperglycemia	22	10.6	3	1.5	12	5.8
Hypophosphatemia	11	5.3	1	0.5	13	6.3
Hypokalemia	7	3.4	0	0.0	3	1.4
Creatinine increased	6	2.9	1	0.5	7	3.4
Hyperlipemia	6	2.9	2	1.0	16	7.7
Dehydration	5	2.4	8	4.0	11	5.3
Peripheral edema	5	2.4	0	0.0	0	0.0
Hypercalcemia	4	1.9	5	2.5	2	1.0
Alkaline phosphatase increased	3	1.4	8	4.0	11	5.3
SGOT increased	3	1.4	8	4.0	9	4.3
Weight loss	3	1.4	4	2.0	13	6.3
MUSCULOSKELETAL						
Bone pain	3	1.4	3	1.5	3	1.4
NERVOUS SYSTEM						
Somnolence	3	1.4	5	2.5	2	1.0
RESPIRATORY						
Dyspnea	17	8.2	10	5.0	19	9.1
Pleural effusion	5	2.4	3	1.5	1	0.5
Pneumonia	5	2.4	4	2.0	8	3.8
SKIN AND APPENDAGES						
Rash	5	2.4	0	0.0	2	1.0
Maculopapular rash	3	1.4	0	0.0	0	0.0
Pruritic rash	3	1.4	0	0.0	0	0.0
UROGENITAL						
Urinary tract infection	3	1.4	0	0.0	1	0.5

Datasets: ADVERSE.xpt and BASELINE.xpt

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Study 3066K1-304-WW, the incidence of treatment discontinuation was high in all arms over the course of the trial (TEMSR 95.7%, IFN-α 97%, IFN-α/TEMSR 92.8%). The most common reason for treatment discontinuation in the temsirolimus arm was disease progression (73.6%), followed by adverse event (7.2%), symptomatic deterioration (6.7%), and subject request not otherwise specified (3.8%). The rate of discontinuation due to subject request was similar in all three arms. Patients in the IFN-α arm were more than twice as likely as those in the temsirolimus arm to discontinue treatment due to an adverse event (14.5% versus 7.2%) or symptomatic deterioration (14% versus 6.7%). Discontinuation due to death was least common in the temsirolimus arm (2.9%), higher in the IFN-α arm (5%), and highest in the combination arm (8.2%). These data are shown in the sponsor's table below.

Table 7.6 Treatment Discontinuation by Reason (from Sponsor)

Reasons for Treatment Discontinuation in Study 304: Number (%) of Patients

Conclusion Status Reason [a]	IFN n=200	TEMSR 25 mg n=208	TEMSR 15 mg/ IFN n=208
Discontinued	194 (97.0)	199 (95.7)	193 (92.8)
Disease progression	115 (57.5)	153 (73.6)	100 (48.1)
Adverse event	29 (14.5)	15 (7.2)	42 (20.2)
Symptomatic deterioration	28 (14.0)	14 (6.7)	21 (10.1)
Subject request	6 (3.0)	8 (3.8)	7 (3.4)
Death	10 (5.0)	6 (2.9)	17 (8.2)
Other	4 (2.0)[b]	2 (1.0)[c]	6 (2.9)[d]
Protocol violation	2 (1.0)	1 (0.5)	0

Abbreviations: IFN = interferon; TEMSR = temsirolimus.

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by patient.
b. Other reasons for discontinuation in the IFN arm were lost to follow up, investigator's discretion, patient underwent surgery, and patient's request.
c. Other reasons for discontinuation in the TEMSR arm were disease progression and investigator's decision.
d. Other reasons for discontinuation in the TEMSR/IFN arm were required prohibited treatment (radiation), patient non-compliance, investigator's request (2), general worsening of the patient's health, and disease progression.

7.1.3.2 Adverse events associated with dropouts

In the overall safety population of 616 patients, 14% withdrew from the study due to an adverse event. Within the temsirolimus arm, 7% of patients withdrew due to an AE. Study withdrawal due to AE was much more common in the IFN-α arm (15%) and the combination IFN-α/temsirolimus arm (20%). The most common AEs that resulted in study withdrawal in the

temsirolimus arm included increased creatinine (n=3), asthenia (n=3), anemia (n=2), abdominal pain (n=2), and peripheral edema (n=2). Of note, one patient in the temsirolimus arm withdrew due to a cerebrovascular accident ultimately resulting in death, and one patient withdrew due to dyspnea and lung infiltrates. See Section 7.1.4 and Section 7.3.7 for further discussion of interstitial lung disease associated with temsirolimus use.

7.1.3.3 Other significant adverse events

During labeling discussions, on 5/23/07, Wyeth notified FDA of safety data from a recently terminated Phase 1/2 trial evaluating the combination of Torisel and Sutent in the treatment of advanced RCC. This trial enrolled three patients to the first cohort (Torisel 15 mg IV weekly plus Sutent 25 mg by mouth daily days 1-28 followed by a 2 week rest). Of these three patients in cohort 1, 2 developed dose-limiting toxicities (DLTs). The first DLT was Grade 3/4 erythematous maculopapular rash and the second DLT was cellulitis and gout requiring hospitalization. This information indicates that the combination of Torisel and Sutent at the tested doses was not safe or tolerable. At the time of this review, discussions are ongoing as to whether this information will be in the label document for this submission.

See Section 7.1.4 below.

7.1.4 Other Search Strategies

Interstitial lung disease (ILD, termed pneumonitis, alveolitis, or bronchiolitis) was reported as a TEAE in 5 patients in the temsirolimus arm compared with one patient in the IFN-α arm and one patient in the IFN-α/temsirolimus arm. All but one of these cases were judged at least possibly related to study drug.

To further investigate this safety signal, this reviewer selected from the list of preferred terms TEAEs that could potentially represent pneumonitis, including dyspnea, cough increased, pneumonia, upper respiratory infection, pulmonary physical finding, bronchitis, and wheezing, in addition to pneumonitis, alveolitis, and bronchiolitis. Table 7.7 below shows the relative incidence of these TEAEs by treatment arm.

Reviewer Comment: In addition to the increased incidence of interstitial lung disease (ILD) diagnosed in the temsirolimus arm, patients who received temsirolimus, either alone or in combination with interferon, also experienced an increased incidence of several potentially related pulmonary TEAEs. These data suggest that the true incidence of ILD in patients receiving temsirolimus may have been underestimated and underscores the need for heightened awareness of symptoms that may indicate ILD as larger numbers of patients are exposed to temsirolimus.

Table 7.7 Relative Incidence of Pulmonary Adverse Events That Could Represent Pneumonitis by Treatment Arm (Safety Population)

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Pneumonitis	4	1.9	1	0.5	0	0.0
Alveolitis	1	0.5	0	0	0	0
Bronchiolitis	0	0	0	0	1	0.5
Dyspnea	57	27.4	43	21.5	51	24.5
Cough Increased	53	25.5	29	14.5	48	23.1
Pneumonia	15	7.2	8	4.0	15	7.2
Upper Respiratory Infection	14	6.7	1	0.5	6	2.9
Pulmonary Physical Finding	10	4.8	3	1.5	6	2.9
Wheezing	3	1.4	2	1.0	2	1.0

Datasets: ADVERSE.xpt and BASELINE.xpt

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

There were 25,356 treatment-emergent adverse events in the phase III pivotal trial. Thirty-two percent (32%) of these were in the temsirolimus arm, compared with 27% in the IFN-α arm and 41% in the combination IFN-α/temsirolimus arm.

See also Section 7.1.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Only 11 TEAEs in 9 patients (out of a total of 25,356 TEAEs) were reported by investigators but not assigned a preferred term by the sponsor in the clinical databases. A random audit by this

reviewer demonstrated that verbatim terms for AEs appear to have been appropriately converted by the sponsor into preferred terms using COSTART.

7.1.5.3 Incidence of common adverse events

There were 25,356 treatment-emergent adverse events in the phase III trial. Thirty-two percent (32%) of these were in the temsirolimus arm, compared with 27% in the IFN-α arm and 41% in the combination IFN/temsirolimus arm.

Reviewer Comment: Due to variable reporting by investigators of laboratory abnormalities as adverse events, the incidence of laboratory-related TEAEs under-represents the true incidence of these toxicities. Use of the incidence of abnormal laboratory parameters provides a more accurate and objective picture of the toxicity profile of temsirolimus.

Virtually all patients on all arms experienced toxicities in this study, and most experienced multiple toxicities. TEAEs that occurred in 5% or more of patients in the temsirolimus arm and were more common on the temsirolimus arm than the IFN-α arm included: anemia, rash, pain, hyperlipemia, dyspnea, diarrhea, peripheral edema, hyperglycemia, increased cough, hypercholesterolemia, abdominal pain, stomatitis, constipation, back pain, pruritus, mucositis, thrombocytopenia, nail disorder, epistaxis, pharyngitis, dry skin, acne, rhinitis, hypokalemia, increased alkaline phosphatase, allergic reaction, edema, hypophosphatemia, anxiety, exfoliative dermatitis, urinary tract infection, pneumonia, accidental injury, face edema, hypertension, upper respiratory infection, paresthesia, increased lactic dehydrogenase, pruritic rash, and taste loss.

Please see Table 7.8 below for details.

Reviewer Comment: The most common non-laboratory-related TEAEs in the temsirolimus arm were: rashes, asthenia, mucositis-related events, nausea, edema-related events, anorexia, pain, dyspnea, diarrhea, and cough.

7.1.5.4 Common adverse event tables

Table 7.8 Common Treatment-Emergent Adverse Events (>/= 5% of All Patients on Temsirolimus Arm) in Order of Incidence

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Asthenia	104	50.0	125	62.5	129	62.0
Anemia	94	45.2	83	41.5	127	61.1
Nausea	77	37.0	82	41.0	84	40.4
Rash	77	37.0	11	5.5	34	16.3

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Anorexia	66	31.7	87	43.5	79	38.0
Pain	59	28.4	31	15.5	41	19.7
Hyperlipemia	57	27.4	28	14.0	79	38.0
Dyspnea	57	27.4	43	21.5	51	24.5
Diarrhea	56	26.9	40	20.0	56	26.9
Peripheral edema	56	26.9	16	8.0	34	16.3
Hyperglycemia	53	25.5	22	11.0	35	16.8
Cough increased	53	25.5	29	14.5	48	23.1
Hypercholesteremia	51	24.5	9	4.5	55	26.4
Fever	50	24.0	99	49.5	124	59.6
Abdominal pain	44	21.2	34	17.0	36	17.3
Stomatitis	42	20.2	7	3.5	43	20.7
Constipation	42	20.2	36	18.0	40	19.2
Back pain	41	19.7	28	14.0	30	14.4
Vomiting	40	19.2	57	28.5	62	29.8
Pruritus	40	19.2	16	8.0	23	11.1
Mucositis	39	18.8	10	5.0	48	23.1
Weight loss	39	18.8	49	24.5	66	31.7
Arthralgia	37	17.8	29	14.5	27	13.0
Chest pain	34	16.3	18	9.0	23	11.1
Headache	31	14.9	30	15.0	46	22.1
Taste perversion	31	14.9	13	6.5	18	8.7
Creatinine increased	30	14.4	21	10.5	41	19.7
Infection	29	13.9	9	4.5	30	14.4
Thrombocytopenia	28	13.5	16	8.0	77	37.0
Nail disorder	28	13.5	1	0.5	6	2.9
Epistaxis	25	12.0	7	3.5	27	13.0
Pharyngitis	25	12.0	3	1.5	24	11.5
Insomnia	24	11.5	30	15.0	35	16.8
Dry skin	22	10.6	14	7.0	13	6.3
Acne	21	10.1	2	1.0	6	2.9
Rhinitis	20	9.6	4	2.0	9	4.3
Hypokalemia	19	9.1	7	3.5	13	6.3
Alkaline phosphatase increased	19	9.1	15	7.5	30	14.4
Dizziness	19	9.1	25	12.5	27	13.0
Allergic reaction	18	8.7	1	0.5	12	5.8
Edema	18	8.7	8	4.0	7	3.4
Chills	17	8.2	59	29.5	71	34.1

ADVERSE EVENT	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Hypophosphatemia	17	8.2	4	2.0	21	10.1
SGOT increased	17	8.2	29	14.5	43	20.7
Myalgia	16	7.7	29	14.5	22	10.6
Anxiety	16	7.7	12	6.0	23	11.1
Exfoliative dermatitis	16	7.7	1	0.5	6	2.9
Urinary tract infection	16	7.7	10	5.0	22	10.6
Neutropenia	15	7.2	25	12.5	56	26.9
Pneumonia	15	7.2	8	4.0	15	7.2
Accidental injury	14	6.7	9	4.5	13	6.3
Face edema	14	6.7	1	0.5	10	4.8
Hypertension	14	6.7	7	3.5	12	5.8
Somnolence	14	6.7	21	10.5	14	6.7
Upper respiratory infection	14	6.7	1	0.5	6	2.9
Dry mouth	13	6.3	16	8.0	12	5.8
Leukopenia	13	6.3	34	17.0	64	30.8
Paresthesia	13	6.3	10	5.0	13	6.3
Hypoproteinemia	12	5.8	19	9.5	21	10.1
SGPT increased	12	5.8	14	7.0	14	6.7
Lymphopenia	11	5.3	16	8.0	26	12.5
Hypocalcemia	11	5.3	21	10.5	30	14.4
Lactic dehydrogenase increased	11	5.3	6	3.0	19	9.1
Pruritic rash	11	5.3	1	0.5	3	1.4
Taste loss	11	5.3	4	2.0	5	2.4

Datasets: ADVERSE.xpt and BASELINE.xpt

7.1.5.5 Identifying common and drug-related adverse events

As shown in Table 7.8 above, TEAEs were common in all arms. Adverse events that occurred in 10% or more of patients in the temsirolimus alone arm and in at least twice as many patients as in the IFN-α arm included rash not otherwise specified (37% versus 5.5%), hyperlipemia (27.4% versus 14%), peripheral edema (26.9% versus 8.0%), hyperglycemia (25.5% versus 11%), hypercholesterolemia (24.5% versus 4.5%), stomatitis (20.2% versus 3.5%), pruritus (19.2% versus 8%), mucositis (18.8% versus 5%), taste perversion (14.9% versus 6.5%), infection (13.9% versus 4.5%), nail disorder (13.5% versus 0.5%), epistaxis (12% versus 3.5%), and acne (10.1% versus 1%). These data are shown in Table 7.9 below:

Table 7.9 Adverse Events that Occurred in At Least 10% of Patients in the Temsirolimus Arm and in At Least Twice as Many Patients as in the IFN-α Arm

ADVERSE EVENT	TEMSR N=208		IFN-α N=200	
	N	%	N	%
Rash	77	37.0	11	5.5
Hyperlipemia	57	27.4	28	14.0
Peripheral edema	56	26.9	16	8.0
Hyperglycemia	53	25.5	22	11.0
Hypercholesteremia	51	24.5	9	4.5
Stomatitis	42	20.2	7	3.5
Pruritus	40	19.2	16	8.0
Mucositis	39	18.8	10	5.0
Taste perversion	31	14.9	13	6.5
Infection	29	13.9	9	4.5
Nail disorder	28	13.5	1	0.5
Epistaxis	25	12.0	7	3.5
Acne	21	10.1	2	1.0

Datasets: ADVERSE.xpt and BASELINE.xpt

7.1.5.6 Additional analyses and explorations

See Section 7.4.2.2.

7.1.6 Less Common Adverse Events

See Section 7.1.7.5 for a discussion of cases of renal failure. See Sections 7.3.3 and 7.3.7 for a discussion of cases of bowel perforation and interstitial lung disease.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In Study 3066K1-304-WW, a complete blood count (CBC) was performed weekly, and measurement of coagulation parameters was done monthly during treatment. A chemistry panel, intended to be performed in the fasting state, was performed every 2 weeks while on treatment. After 16 weeks on study, investigators were permitted to decrease the frequency of CBC to every 2 weeks and the frequency of chemistry panels to monthly if clinically appropriate. The sponsor graded all laboratory data collected in the study according to NCI CTC version 3.0 to identify

individual subjects who met criteria for values of potential clinical importance (PCI). Investigators were intended to record as adverse events laboratory abnormalities that were judged to be clinically significant with particular attention to grade 3 or 4 laboratory abnormalities.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Assessment of adverse events related to laboratory abnormalities was performed using the safety population of Study 3066K1-304-WW. Advanced RCC patients have a high background rate of abnormal laboratory values, and Study 3066K1-304-WW was the only one that enrolled advanced RCC patients at the proposed dose for marketing and included an appropriate control group.

7.1.7.3 Standard analyses and explorations of laboratory data

At baseline, more than 95% of patients in each treatment arm had potentially clinically important laboratory abnormalities.

Reviewer Comment: While common in all arms, laboratory abnormalities of all grades, as well as the subset of grade 3 and 4 laboratory abnormalities, were more common during treatment in patients assigned to arms containing temsirolimus than in those receiving IFN-α alone (Temsirolimus 100% and 77.9%, IFN-α/temsirolimus 99% and 82.7%, IFN-α 97.5% and 72%, respectively).

As discussed in the analyses of common and grade 3/4 TEAEs above, certain laboratory abnormalities, including decreased hemoglobin, increased glucose, increased total cholesterol and triglycerides, decreased lymphocyte count, increased creatinine, decreased platelet count, and decreased neutrophil count, occurred more commonly among patients receiving temsirolimus than among those receiving IFN-α. The relative incidence of selected potentially clinically important changes in laboratory parameters by arm is shown in Table 7.10 below.

Table 7.10 Incidence of Selected Abnormalities in Laboratory Parameters of Special Interest by Treatment Arm and NCI CTC Grade on Treatment

LABORATORY	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Any abnormality						
Overall	208	100.0	195	98	206	99
Grade 3/4	162	78	144	72	172	83
CHEMISTRY						
Alkaline Phosphatase Increased						
Overall	141	68	111	56	137	66
Grade 3/4	7	3	13	7	16	8

LABORATORY	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
AST Increased						
Overall	79	38	103	52	146	70
Grade 3/4	5	2	14	7	13	6
Bilirubin Increased						
Overall	16	8	25	13	21	10
Grade 3/4	2	1	4	2	0	0
Calcium Decreased						
Overall	82	39	83	42	126	61
Grade 3/4	6	3	5	3	4	2
Calcium Increased						
Overall	46	22	46	23	34	16
Grade 3/4	8	4	12	6	8	4
Cholesterol Increased						
Overall	181	87	95	48	152	73
Grade 3/4	5	2	2	1	5	2
Creatinine Increased						
Overall	119	57	97	49	119	57
Grade 3/4	7	3	2	1	6	3
Glucose Increased						
Overall	186	89	128	64	158	76
Grade 3/4	33	16	6	3	21	10
Phosphorus Decreased						
Overall	99	48	54	27	103	50
Grade 3/4	38	18	17	9	34	16
Potassium Increased						
Overall	52	25	68	34	49	24
Grade 3/4	10	5	9	5	7	3
Triglycerides Increased						
Overall	173	83	144	72	176	85
Grade 3/4	92	44	69	35	75	36
HEMATOLOGY						
Hemoglobin Decreased						
Overall	195	94	180	90	201	97
Grade 3/4	41	20	43	22	75	36
Leukocytes Decreased						
Overall	67	32	93	47	144	69
Grade 3/4	1	1	11	6	22	11
Lymphocytes Decreased						
Overall	149	72	136	68	176	85

LABORATORY	TEMSR N=208		IFN-α N=200		IFN-α/TEMSR N=208	
	N	%	N	%	N	%
Grade 3/4	33	16	48	24	80	38
Neutrophils Decreased						
Overall	70	34	63	32	88	42
Grade 3/4	10	5	19	10	38	18
Platelets Decreased						
Overall	84	40	51	26	135	65
Grade 3/4	3	1	0	0	18	9

Datasets: LABTEST 1-6.xpt, BASELINE.xpt, and DEMOWIDE.xpt

7.1.7.4 Additional analyses and explorations

See Section 7.4.2.2.

7.1.7.5 Special assessments

As shown in Table 7.10, abnormalities in liver function did not appear to be increased overall for patients receiving temsirolimus monotherapy compared to patients receiving IFN-α alone. While elevations in alkaline phosphatase were more common in the temsirolimus-containing arms (68% and 66% for temsirolimus and IFN-α/temsirolimus arms, respectively) than in the IFN-α arm (56%), grade 3/4 abnormalities occurred less often in patients receiving temsirolimus (3%) than in patients receiving IFN-α (7%). Elevations in aspartate aminotransferase occurred less often in the temsirolimus alone arm than in either the combination arm or the IFN-α arm (38%, 70%, and 52%, respectively). Elevations in total bilirubin were also less common in the temsirolimus arm (8%) than in the IFN-α/temsirolimus arm (13%) or the IFN-α arm (11%).

Reviewer Comment: Elevations of serum creatinine were more common in patients who received temsirolimus either alone (57%) or in combination with IFN-α (57%) than in patients who received IFN-α alone (49%). Grade 3 and 4 elevations in creatinine were also more common for patients in the temsirolimus arm (3%) or the combination arm (3%) than for patients in the IFN-α arm (1%). Abrupt declines in renal function that were not clearly related to disease progression, some resulting in death, have occurred in association with temsirolimus use.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including weight, were collected at the screening visit, every 4 weeks while on treatment, and at the time of study withdrawal. Summary analyses of vital signs and body weight were not provided by the sponsor.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable. Only Study 3066K1-304-WW included the population of patients with advanced renal cell carcinoma and an appropriate control arm (interferon alone).

7.1.8.3 Standard analyses and explorations of vital signs data

Elevations in blood pressure occurred more commonly in patients receiving temsirolimus either alone or in combination with IFN-α than in patients who received IFN-α alone. Treatment-emergent adverse events of hypertension occurred in 14 patients (6.7%) in the temsirolimus arm and 12 patients (5.8%) in the IFN-α/temsirolimus arm compared with only 7 patients (3.5%) in the IFN-α arm. Three patients (1.4%) in the temsirolimus arm experienced a grade III or IV TEAE related to hypertension compared with 1 patient (0.5%) in the IFN-α/temsirolimus and no patients (0%) in the IFN-α arm.

Other adverse events related to changes in vital signs were similar between treatment arms.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results
From sponsor:
"Based on ECG assessments for 84 cancer patients and 36 healthy subjects who received temsirolimus, there was no evidence for an effect of single-agent temsirolimus on the QT/QTc interval or for any clinically significant arrhythmias related to QT/QTc changes. However, given the relatively modest number of individuals tested, a small effect of temsirolimus on the QT/QTc interval cannot be definitively ruled out."

In the phase 3 trial, electrocardiograms were performed at baseline and at the withdrawal visit at all study sites. These ECGs were obtained once and interpreted by the investigator. The

protocol was later amended for patients enrolling at US and Canadian sites. For patients who enrolled on the amended protocol, ECGs were performed in triplicate at the screening visit; during cycle 1 immediately prior to the first dose of study drug; during cycle 1 just prior to completion of temsirolimus infusion or just after IFN-α infusion; 3 months after the first dose of temsirolimus just prior to the completion of the temsirolimus infusion or just after IFN-α infusion (time point selected to assess any effect on QT/QTc interval after steady-state concentrations of temsirolimus had been achieved); and at the final evaluation. These ECGs were read manually with intervals measured by a third-party central laboratory. A total of 39 patients (IFN-α n=8, TEMSR n=18, IFN-α/TEMSR n=13) enrolled on the amended protocol and had ECGs obtained in triplicate on the schedule detailed above.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable. Only Study 3066K1-304-WW included the population of patients with advanced renal cell carcinoma and an appropriate control arm (interferon alone).

7.1.9.3 Standard analyses and explorations of ECG data

The criteria used by the sponsor to identify individuals with potentially clinically important (PCI) values for QT/QTcF interval were:

1. men with absolute value >450 milliseconds (msec) or women with absolute value >470 msec with an increase > 30 msec;
2. men and women with increase > 60 msec, regardless of absolute value;
3. men and women with absolute value > 500 msec.

There was 1 patient in the temsirolimus arm with longer than normal QTcF after the first dose, but this did not represent an increase from baseline. There were no other patients with a longer than normal QTcF. Among patients with a normal QTcF, there were 2 who experienced an increase of greater than 60 msec: patient 322001 in the temsirolimus arm at the 3 month time point and patient 001006 in the IFN-α/temsirolimus arm at the withdrawal visit. Both patients had concomitant electrolyte abnormalities (hypokalemia or hypocalcemia) and medication use (ondansetron, paroxetine) that could have potentially contributed to QTc prolongation. There were no patients with QTcF of greater than 500 msec after dosing. There were no dropouts for ECG abnormalities.

7.1.9.4 Additional analyses and explorations

Not applicable. See Section 7.1.9.1.

7.1.10 Immunogenicity

Immunogenicity studies have not been performed with temsirolimus.

7.1.11 Human Carcinogenicity

No animal carcinogenicity study has been conducted with temsirolimus given the proposed indication for advanced renal cell carcinoma. Of note, temsirolimus is rapidly converted to sirolimus in humans. Sirolimus was observed to be carcinogenic in animal studies, and there is a boxed warning related to carcinogenicity in the current sirolimus package insert.

From the existing approved label for sirolimus:
"Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared with controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males), were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group."

7.1.12 Special Safety Studies

A phase I study in healthy subjects to assess the effect of temsirolimus on QT/QTc interval was initiated shortly before the data lock date of 05/30/2006 and is ongoing, and data have not yet been provided by the sponsor at the time of this review.

A study of temsirolimus in patients with hepatic impairment is also ongoing through the National Cancer Institute (NCI), and data have not yet been provided by the sponsor.

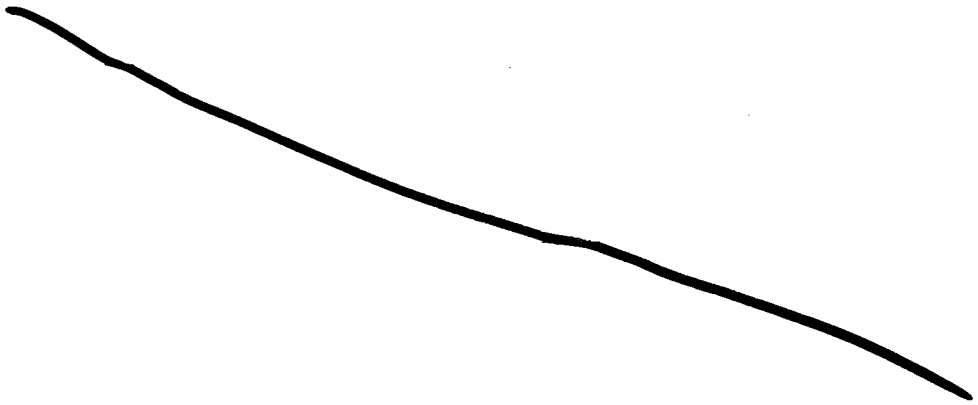
7.1.13 Withdrawal Phenomena and/or Abuse Potential

Temsirolimus is not associated with withdrawal or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

From the sponsor:

"Temsirolimus has been shown to have an embryocidal effect (or other adverse effect) in rats when given at 1.1 times the human dose and to be teratogenic and have an embryocidal effect (or other adverse effects) in rabbits when given at 1.4 times the human dose. There are no adequate and well-controlled studies in pregnant women.



7.1.15 Assessment of Effect on Growth

Not applicable. A phase I study in pediatric patients is ongoing, but data have not yet been provided by the sponsor.

7.1.16 Overdose Experience

There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients with cancer in phase I and II trials with repeated intravenous doses as high as 220 mg/m^2. The risk of several serious adverse events, including thrombosis, bowel perforation, pneumonitis, seizure, and psychosis, is increased with doses of TORISEL greater than 25 mg.

7.1.17 Postmarketing Experience

Not applicable. Temsirolimus has never been marketed before in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 7.11 Safety Population Groupings for Clinical Studies of Intravenous Temsirolimus (from Sponsor)

Safety Population Groupings for Clinical Studies of Intravenous Temsirolimus

Population Group	Studies Included	Temsirolimus Dose(s) and Regimen	No. Treated Study Subjects
Advanced RCC patients treated with single-agent temsirolimus	3066K1-304-WW, -200-US	25 mg once weekly	244
Advanced RCC patients treated with temsirolimus in combination with IFN	3066K1-304-WW, -124-US	15 mg once weekly with IFN 6 MU or 9 MU 3 times weekly	253
Advanced RCC patients treated with single-agent IFN	3066K1-304-WW	18 MU 3 times weekly	200
Advanced RCC, prostate cancer, and breast cancer patients treated with higher temsirolimus doses	3066K1-200-US, -201-US, -203-EU	75 mg or 250 mg once weekly	199
Patients with advanced solid tumors treated with temsirolimus on alternate dosing schedules	3066K1-100-US, -101-EU	≤15 mg/ m^2, 15 mg/ m^2, or >15 mg/m^2 once weekly or once daily for 5 days every 2 weeks[a]	128
Healthy subjects who received single temsirolimus doses	3066K1-133-US, -145-US, -148-US, -149-US, -151-US	≤25 mg or 25 mg	92

Abbreviations: IFN = interferon-α; RCC = renal cell carcinoma

a. A 15 mg/m^2-dose corresponds to approximately a 25-mg dose, using a conversion factor of 1.8 m^2 for average adult body surface area.

Please also refer to Section 4.1 and 4.2.

7.2.1.2 Demographics

All patients had histologically-confirmed, advanced RCC. The 3 treatment arms were appropriately balanced for demographic and other baseline characteristics. The median age was 59 years (range, 23-86 years). The majority of subjects were male (69.0%) and Caucasian (91.1%). Most patients (82.6%) had a borderline Karnofsky performance score (KPS) of 60 to 70. In 66.9% of patients, a nephrectomy had been performed, and 20.8% of patients had received palliative radiation therapy prior to study entry. No patient had taken prior systemic therapy for RCC. A total of 79.7% of patients had metastases involving more than 1 organ or site at study enrollment; lung metastases were present in 74.9%, liver metastases were present in 28%, and bony involvement was present in 42.5%. Brain metastases were uncommon, present in only 4.5% of subjects at baseline.

Table 7.12 Demographic and Baseline Characteristics, ITT Population (From Sponsor)

Demographic and Other Baseline Characteristics in ITT Population

Characteristic.n (%)	IFN (n=207)	TEMSR 25 mg (n=209)	TEMSR 15 mg/IFN (n=210)	Total (n=626)	TEMSR 25 mg p-value[a]	TEMSR 15 mg/IFN p-value[a]
Age, years					0.3977	0.7081
n	207	209	210	626		
Mean	59.2	58.7	59.3	59.1		
SD	10.4	10.0	9.8	10.1		
Median	60.0	58.0	59.0	59.0		
Min, Max	23.0, 86.0	32.0, 81.0	32.0, 82.0	23.0, 86.0		
<65 years	142 (68.6)	145 (69.4)	153 (72.9)	440 (70.3)	0.8636	0.3393
>=65 years	65 (31.4)	64 (30.6)	57 (27.1)	186 (29.7)		
Sex (n, %)					0.2712	0.5842
Female	59 (28.5)	70 (33.5)	65 (31.0)	194 (31.0)		
Male	148 (71.5)	139 (66.5)	145 (69.0)	432 (69.0)		
Race (n, %)					0.6044	0.9119
White	191 (92.3)	186 (89.0)	193 (91.9)	570 (91.1)		
Asian	4 (1.9)	6 (2.9)	3 (1.4)	13 (2.1)		
Black	8 (3.9)	9 (4.3)	8 (3.8)	25 (4.0)		
Other	4 (1.9)	8 (3.8)	6 (2.9)	18 (2.9)		
Weight, kg					0.6037	0.7507
n	204	207	208	619		
Mean	76.0	76.5	75.1	75.9		
SD	16.9	15.3	13.9	15.4		
Median	74.0	76.0	74.0	75.0		
Min, Max	35.0, 159.7	38.5, 135.1	42.0, 121.5	35.0, 159.7		
Unknown	3	2	2	7		
Height, cm					0.4791	0.1849
n	204	207	206	617		
Mean	170.9	170.0	169.6	170.2		
SD	9.3	9.7	9.0	9.4		
Median	171.0	171.0	170.0	170.2		
Min, Max	142.2, 194.0	137.2, 195.0	149.9, 194.0	137.2, 195.0		
Unknown	3	2	4	9		
Karnofsky score (n, %)					0.4364	0.5827
<60	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)		
60-70	171 (83.0)	168 (80.4)	177 (84.3)	516 (82.6)		
>70	34 (16.5)	41 (19.6)	33 (15.7)	108 (17.3)		
Unknown	1	0	0	1		
Region[b] (n, %)					0.9967	0.9795
Region 1	61 (29.5)	61 (29.2)	62 (29.5)	184 (29.4)		
Region 2	43 (20.8)	44 (21.1)	42 (20.0)	129 (20.6)		
Region 3	103 (49.8)	104 (49.8)	106 (50.5)	313 (50.0)		
Prior nephrectomy (n, %)					0.8893	0.9988
No	68 (32.9)	70 (33.5)	69 (32.9)	207 (33.1)		
Yes	139 (67.1)	139 (66.5)	141 (67.1)	419 (66.9)		

7.2.1.3 Extent of exposure (dose/duration)

From the sponsor:
"Of the 208 patients treated in the temsirolimus arm, 49.5% of patients received temsirolimus for up to 16 weeks, 21.7% received temsirolimus for between 16 and 32 weeks, and 15.9% received temsirolimus for between 32 and 48 weeks (Table 10.1.2-1). Thirteen percent (13.0%) of patients

remained on temsirolimus treatment for more than 48 weeks. The median time on treatment was 17 weeks (range, 1-126 weeks). The distribution of time on treatment was skewed because a number of patients were able to remain on treatment for a long time; the mean time on treatment was 25.4 weeks with a wide standard deviation of 23 weeks."

"Overall, the median duration on treatment was longer in the temsirolimus arm (17 weeks) than in the IFN-α arm (8 weeks). Patients in the combination arm had a median duration of treatment of 12 weeks for IFN-α and 15 weeks for temsirolimus. Patients in the temsirolimus arm were able to receive almost the full intended dose (median relative dose intensity 0.99), while patients in the combination arm received 75% of the planned dose of temsirolimus and roughly 75% of the maximum planned dose of IFN-α (4.5 MU 3 times weekly versus 6.0 MU 3 times weekly). The median exposure in the IFN-α arm was roughly half of the maximum planned exposure (9.5 MU 3 times weekly versus 18 MU 3 times weekly)."

Table 0.13 Extent of Exposure to Interferon-Alfa (from Sponsor)

Extent of Exposure to Interferon-Alfa

Parameter	IFN n=200	TEMSR 15 mg / IFN n=208
No. patients treated, n (%)	200 (100)	207[a] (99.5)
Duration of treatment[b,c], n (%) (weeks)		
0 to ≤ 8 weeks	102 (51)	74 (35.7)
8 to ≤ 16 weeks	43 (21.5)	47 (22.7)
16 to ≤ 24 weeks	16 (8)	25 (12.1)
24 to ≤ 32 weeks	17 (8.5)	20 (9.7)
32 to ≤ 40 weeks	3 (1.5)	8 (3.9)
40 to ≤ 48 weeks	2 (1)	9 (4.3)
>48 weeks	17 (8.5)	24 (11.6)
Duration of treatment (weeks)		
Mean	16.0	21.9
SD	20.1	23.6
Median	8.0	12.0
Min, max	1.0 , 124.0	1.0 , 138.0
No. doses per week		
Mean	2.7	2.6
SD	0.4	0.4
Median	2.9	2.7
Min, max	1.0 , 3.0	1.3 , 3.6
Total exposure[d] (MU)		
Mean	589.2	281.1
SD	856.6	300.7
Median	243.0	159.0
Min, max	6.0 , 5058.0	6.0 , 1629.0
Dose intensity[e] (MU/week)		
Mean	30.2	13.1
SD	14.2	3.1
Median	28.5	13.5
Min, max	3.0 , 55.2	5.0 , 19.8

Abbreviations: MU = Million units.
a. As of 30 May 2006, 1 patient in the TEMSR 15 mg/IFN treatment group (027001) was listed in the database as having received only temsirolimus. However, the patient had received 2 doses of IFN during study week 1, as per protocol. This information was provided in a response to a query that was outstanding as of the data cutoff date of 30 May 2006. See Section 14.0, Clinical Data Report Errata.
b. Percentages are based on number of patients who received IFN in each treatment group.
c. Duration of treatment in weeks is defined as CEILING((LAST DOSE DATE - FIRST DOSE DATE + 1) / 7 - 0.001).
d. Total exposure is defined as the sum of all doses received.
e. Dose intensity is defined as the total exposure divided by the total number of weeks on treatment.
SMED4_IFN_RDI - 13JUN06 14:27

Table 7.14 Number (%) of Patients Treated with Interferon by Maximum Dose Received (from Sponsor)

Number (%) of Patients Treated with Interferon by Maximum Dose Received

Category, n (%)	IFN n=200[a]	TEMSR 15 mg IFN n=208[b]
No. patients treated	200 (100.0)	207[c] (99.5)
Maximum dose[d,e]		
3 MU	19 (9.5)	10 (4.8)
4.5 MU	0	2 (1.0)
6 MU	2 (1.0)	192 (92.8)
9 MU	43 (21.5)	0
18 MU	134 (67.0)	1 (0.5)[f]

a. Two (2) patients (018001 and 565004) in IFN dose group did not receive 3 consecutive doses of IFN.
b. Two (2) patients (016011 and 058003) in the combination arm did not receive 3 consecutive doses of IFN.
c. As of 30 May 2006, 1 patient in the TEMSR 15 mg/IFN treatment group (022001) was listed in the database as having received only temsirolimus. However, the patient had received 2 doses of IFN during study week 1, as per protocol. This information was provided in a response to a query that was outstanding as of the data cutoff date of 30 May 2006. See Section 14.0, Clinical Data Report Errata.
d. Patients received maximum dose for at least 3 consecutive doses.
e. Percentages are based on number of patients who received IFN in each treatment group.
f. Medication error in patient 561002. See text.

SMED4_IFN_MAX - 14JUN06 11:31

Table 7.15 Extent of Exposure to Temsirolimus (from Sponsor)

Extent of Exposure to Temsirolimus

Parameter, n (%)	TEMSR 25 mg n=208	TEMSR 15 mg/IFN n=208 [a]
No. of patients treated (n, %)	208 (100)	200 (96.2)
Duration of treatment [b,c] (n, %)		
>0 to ≤ 8 weeks	56 (26.9)	63 (31.5)
>8 to ≤ 16 weeks	47 (22.6)	48 (24)
>16 to ≤ 24 weeks	27 (13)	26 (13)
>24 to ≤ 32 weeks	18 (8.7)	20 (10)
>32 to ≤ 40 weeks	16 (7.7)	9 (4.5)
>40 to ≤ 48 weeks	17 (8.2)	9 (4.5)
>48 weeks	27 (13)	25 (12.5)
Duration of treatment (weeks)[c]		
Mean	25.4	23.3
SD	23.0	24.4
Median	17.0	15.0
Min, max	1.0 , 126.0	1.0 , 138.0
Total exposure[d] (mg)		
Mean	581.7	260.6
SD	542.3	287.1
Median	380.0	135.0
Min, max	25.0 , 3125.0	2.4 , 1970.0

Table 7.16 Dose Intensity of Exposure to Temsirolimus (from Sponsor)

Extent of Exposure to Temsirolimus

Parameter, n (%)	TEMSR 25 mg n=208	TEMSR 15 mg/IFN n=208 [a]
Dose intensity[e] (mg/week)		
Mean	23.1	10.9
SD	3.1	2.6
Median	24.7	11.3
Min, max	10.8 , 29.2	1.2 , 15.0
Relative dose intensity[f]		
Mean	0.92	0.73
SD	0.12	0.17
Median	0.99	0.75
Min, max	0.43 , 1.2	0.08 , 1.0

a. Eight (8) patients in the TEMSR 15 mg/IFN treatment group never received temsirolimus.
b. Percentages are based on number of patients receiving temsirolimus in each treatment group.
c. Duration of treatment in weeks is defined as CEILING((LAST DOSE DATE - FIRST DOSE DATE + 1) / 7 + 0.001).
d. Total exposure is defined as the sum of all doses received.
e. Dose intensity is defined as the total exposure divided by the duration of treatment in weeks.
f. Relative dose intensity is defined as the actual total exposure divided by the expected total exposure.
SMED4_TEMSR_RDI - 12JUN06 09:41

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The primary safety review has been limited to data from the phase 3 trial because of the high background rate of adverse events in patients with advanced renal cell carcinoma and the different doses and lack of appropriate controls in other studies of temsirolimus included in the safety database. The other clinical studies included in the safety database have been used for investigation of certain rare, serious toxicities such as interstitial lung disease and bowel perforation.

7.2.2.2 Postmarketing experience

Not applicable. Temsirolimus has never been marketed before in any country.

7.2.2.3 Literature

See Section 8.6.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with temsirolimus is sufficient to perform the safety review. The registration trial was a randomized, open-label, active-control trial with 3 treatment arms. The dose and duration of exposure are detailed in the sponsor narrative/tables incorporated in Section 7.2.1.3. The design and exposure were adequate to assess safety in the intended treatment population of patients with advanced RCC for whom existing treatment options are only modestly effective and are associated with considerable toxicity.

While a minimum acceptable performance status (Karnofsky score of 60 or greater) was specified, eligibility criteria also included that patients must have at least 3 of 6 indicators of poor prognosis including: less than 1 year from time of initial RCC diagnosis to randomization ; Karnofsky performance status of 60 or 70; hemoglobin less than the lower limit of normal; corrected calcium > 10 mg/dL; lactate dehydrogenase > 1.5 times the upper limit of normal (ULN); and more than one metastatic site of disease (defined as different tissues or organs with metastasis).

Patients were permitted to enroll with metabolic abnormalities, including a total bilirubin up to 1.5 times the upper limit of normal (ULN); aspartate transaminase (AST) up to 3 times the ULN (or 5 times the ULN if hepatic metastases were present); and serum creatinine up to 1.5 times the ULN.

Reviewer Comment: The study eligibility criteria selected for patients who had a uniformly poor prognosis and a significant number of medical comorbidities, which is likely to be representative of the patient population who will receive temsirolimus once marketed.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Section 5.

7.2.5 Adequacy of Routine Clinical Testing

The nature and timing of clinical and laboratory monitoring of patients for adverse event data collection are detailed in Section 7.1 and were adequate for the expected toxicities of treatment with interferon and temsirolimus.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Section 5.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A phase I study in healthy subjects to assess the effect of temsirolimus on QT/QTc interval was initiated shortly before the data lock date of 05/30/2006 and is ongoing, and data have not yet been provided by the sponsor.

A study of temsirolimus in patients with hepatic impairment is ongoing by the NCI, and data have not yet been provided by the sponsor.

The sponsor has appropriately identified the following potential safety concerns in the temsirolimus development program: hyperglycemia, dypsnea, interstitial lung disease (ILD), infections, and drug-drug interactions. A pharmacovigilance and risk minimization plan for these issues, as well as for risk of QT prolongation and use by hepatically-impaired patients, have been briefly outlined by the sponsor. This includes: careful labeling, proactive collection of additional data in a systematic manner to identify and characterize potential risk factors and subpopulations at greater risk for these AEs, and provision of routinely scheduled reports to regulatory authorities.

In addition to the safety concerns outlined by the sponsor, rare cases of bowel perforation occurring in association with drug-related mucositis were identified in the safety database [redacted]

Given the very high incidence of hyperlipemia, including grade 3 and 4 hypertriglyceridemia, [redacted]

Finally, cases of rapidly-progressive and often dialysis-refractory acute renal failure, have been reported in association with temsirolimus use [redacted]

Please also see Section 7.1.9.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data for Study 3066K1-304-WW in advanced renal cell carcinoma were adequate for the review. All TEAEs were reported for 615 out of 616 total patients in the safety population of the study. As of the data lock date of 05/30/2006, reported

AEs had been converted into preferred terms for 25,347 out of 25,356 total AEs on study. Thus, missing data were rare and felt unlikely by this reviewer to alter the safety conclusions in a meaningful way.

7.2.9 Additional Submissions, Including Safety Update

The Safety Update submitted by the sponsor on 01/04/2007 includes safety data from Study 3066K1-304-WW that became available after the original data cutoff of 05/30/2006 through the safety update data cutoff date of 10/02/2006. Case report forms were provided for any patients who newly met a criterion of death, discontinuation due to an adverse event, or occurrence of an SAE.

As of the 10/02/2006 data cutoff, a total of 1163 patients have received IV temsirolimus in 20 clinical studies in the Wyeth temsirolimus development program. The data from the Safety Update do not suggest any significant changes in the safety profile of temsirolimus compared with the original NDA submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Metabolic Derangements

Abnormal electrolytes and other metabolic derangements were common in the study, occurring in more than half of patients, and were judged to be treatment-related by the investigator in the majority of cases. Several TEAEs related to metabolic laboratory abnormalities were more common in patients receiving temsirolimus. These included hypercholesterolemia (25% in the temsirolimus arm, 5% in the IFN-α arm, and 26% in the combination IFN-α/temsirolimus arm), hyperlipemia (27%, 14%, and 38%), hyperglycemia (26%, 11%, and 17%), hypophosphatemia (8%, 2%, and 10%), and hypokalemia (9%, 4%, and 6%).

The incidence of abnormal laboratory values for the same parameters was much higher than the reported incidence of TEAEs associated with the laboratory abnormalities. This is due in part to the fact that not all laboratory abnormalities were treatment-emergent. In addition, investigators were instructed to report as AEs only those laboratory abnormalities that were deemed clinically significant, and the threshold for reporting laboratory abnormalities as AEs varied among investigators. See Section 7.1.7 for a more detailed discussion.

Reviewer Comment: Despite the very high incidence of hypertriglyceridemia (83%), including a 44% incidence of grade 3 or 4 hypertriglyceridemia on treatment, there were no cases of pancreatitis reported in the study. There was only one TEAE of elevated amylase, which was grade 1 and occurred in the combined IFN-α/temsirolimus arm, although amylase and lipase were not routinely checked. Of note, the incidence of both overall and grade 3/4 abdominal pain was higher in the temsirolimus arm (21% and 4.3%, respectively) compared with the IFN-α arm (17% and 1.5%, respectively). It is possible that some of this increased incidence of abdominal pain was due to pancreatitis that was not diagnosed.

7.3.2 Hemorrhagic events

The incidence of hemorrhagic TEAEs was greater in patients who received temsirolimus alone (25%) or in combination with IFN-α (25%) than in those who received IFN-α alone (17%). The most common bleeding event was epistaxis, which was observed in 12% of patients in the temsirolimus arm compared with 4% of patients in the IFN-α arm. All cases of epistaxis that occurred in the TEMSR arm were mild in severity.

There were only a small number of more serious hemorrhagic events reported which failed to demonstrate a consistent trend in terms of treatment arm.

Of note, while relatively infrequent, TEAEs related to prolongation of the activated partial thromboplastin time (aPTT) were observed more commonly in patients receiving temsirolimus (3.8%) than in patients receiving IFN-α (1.5%). Thrombocytopenia was also more common among patients on the temsirolimus arm (14%) compared with the IFN-α arm (8%). These laboratory abnormalities may in part explain the increased incidence of bleeding events in patients who received temsirolimus.

7.3.3 Mucositis-Related Events, including Bowel Perforation

Mucositis-related events (defined as any of the following: apthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis) were markedly increased among patients receiving temsirolimus, either alone (41%) or in combination with IFN-α (44%), compared with those assigned to IFN-α alone (10%) and were judged to be treatment-related by the investigator in most cases. While increased in the temsirolimus arm (6%) compared with the IFN-α arm (0%), grade 3 or 4 mucositis-related events were relatively uncommon.

Of note, seven cases of bowel perforation in association with temsirolimus use were identified throughout the entire safety database and are discussed in further detail below.

Two cases of bowel perforation in association with temsirolimus use were reported in Study 3066K1-103-EU, a phase 1 dose-escalation study that tested a regimen of temsirolimus 45 mg/m2 IV weekly along with bolus 5-fluorouracil and leucovorin in a total of 28 patients with advanced cancer. The first (Patient ID: 883/28) was a 55 year old man with metastatic cholangiocarcinoma who received his first dose of TEMSR on 02/05/2001. On [redacted] he developed fever and stupor. One week later, he developed grade 4 abdominal pain with a metabolic acidosis. He died the following day, on day [redacted] of treatment. An autopsy demonstrated grade 4 mucositis with associated perforations in the rectal musosa judged to be definitely related to test article. There were no signs of ischemic vasculitis. The second (Patient ID: 883/11) was a 56 year old man with metastatic esophageal cancer who received his first dose of temsirolimus on 03/20/2000. On day [redacted] of treatment, he presented with an acute abdomen and septic shock, which was suspected to be due to intestinal perforation. No surgery or autopsy was performed. The cause of death was listed as intestinal perforation and sepsis related to test article.

One case of bowel perforation occurred in Study 3066K1-131, a single-agent dose-escalation trial in patients with advanced cancer. The patient (Patient ID: 101) was a 61 year old man with metastatic colon cancer who had a history of associated ileus and abdominal adhesions. He began treatment with temsirolimus 15 mg IV weekly on 11/05/2002. His week 2 dose due on 11/12/2002 was held because of fever. On [redacted] he complained of abdominal distention and pain, loose stools, and anorexia. A CT scan showed dilatation of the small bowel, adhesions, and suspected disease progression, as well as intraperitoneal leakage of contrast. He was hospitalized and underwent laparotomy, which revealed "coalescent small intestine in the pelvic region, edematous hypertrophy in mesenteric area, and perforation close to terminal ileum." By the operative report and pathology report, there was no visible peritoneal cancer involvement, nor any evidence of cancer lesion at the perforation site. The patient recovered and was discharged from the hospital on [redacted] He received no further treatment with temsirolimus and was withdrawn from the study. The AE was judged to be unlikely related to test article.

One case of bowel perforation was reported in Study 3066A3-206-WW, which tested a regimen of weekly oral methotrexate with daily oral temsirolimus or placebo in patients with active rheumatoid arthritis. The patient (Patient ID: 079) was a 65 year old woman with rheumatoid arthritis receiving indomethacin and prednisone (doses unknown) who was assigned to the methotrexate 7.5 mg weekly and temsirolimus 4 mg daily arm. She began study treatment on 05/04/2004. At week 2, she reportedly moderately severe diarrhea that was thought probably related to test article and treated with Imodium. On [redacted] she was hospitalized with abdominal pain, diarrhea, and fever and was noted to have a pneumoperitoneum. At surgery, she was found to have perforated sigmoiditis and required a sigmoidectomy, terminal left iliac colostomy, and drainage, as well as intravenous antibiotics. She received no further treatment with temsirolimus and was withdrawn from the study because of the AE, which was judged to be possibly related to test article.

One case of bowel perforation was reported in Study 3066K1-305, an ongoing phase 3 trial testing two dose levels of weekly IV temsirolimus versus standard therapy in patients with

mantle cell lymphoma. The patient (Patient ID: 045001) was a 56 year old man with relapsed mantle cell lymphoma, including a metastasis involving the distal colon/rectum, but no prior history of peptic ulcer disease, who received his first dose of temsirolimus 175 mg iv on 03/10/2006. He received the same dose at week 2, then had the drug held for 1 week and restarted at a lower dose (75 mg iv weekly) for weeks 4-5 due to unknown reasons. His week 6 dose due on 04/13/2006 was also held for unknown reasons. He presented to the ER on [redacted] with acute onset of severe right upper quadrant abdominal pain and was noted to be hypotensive and tachycardic. A CT scan showed perforated ulcers in the duodenum with extravasation of contrast. He and the family declined urgent surgery, and he died in the hospital on [redacted] The investigator judged the AE to be possibly related to test article.

Finally, two cases of bowel perforation were reported in Study 3066K1-304-WW, one in the temsirolimus arm (Patient ID: 016019) and one in the IFN-α/temsirolimus (Patient ID: 508024) arm. Narratives for these patients appear in Section 7.1.1.

Reviewer Comment: Mucositis-related events were much more common in patients receiving temsirolimus alone (41%) or in combination with interferon (44%) than in patients receiving interferon (10%). While grade 3/4 cases of mucositis were relatively uncommon in the temsirolimus arm (6%), there were seven cases of bowel perforation in association with temsirolimus use identified in the entire safety database. Four of these seven cases were fatal. An autopsy on one of the patients demonstrated grade 4 mucositis with multiple perforations in the rectal mucosa. [redacted]

7.3.4 Dermatologic Events

Dermatologic TEAEs were very common among patients taking temsirolimus and appear to be dose-related. Observed rashes were coded using a variety of preferred terms including: rash, pustular rash, vesicobullous rash, pruritic rash, maculopapular rash, eczema, exfoliative dermatitis, and pustular rash. The most common dermatological manifestation was rash, not otherwise specified.

Reviewer Comment: The percentage of patients experiencing any rash-related TEAE other than acne was 57% in the temsirolimus alone arm compared with 7% in the IFN-α alone arm. Most rashes were mild in severity. Five percent (5%) of patients receiving temsirolimus had a grade 3 or 4 rash, compared with 0% in the IFN-α arm. For most of these patients, this manifested as exfoliative dermatitis.

In addition, 10% of patients in the temsirolimus arm experienced a TEAE of acne compared with 1% in the temsirolimus arm. There were no cases of grade 3 or 4 acne in either arm.

7.3.5 Renal Events

Renal TEAEs that occurred in at least 5% of patients in the temsirolimus arm and were more common among patients receiving temsirolimus included: peripheral edema (27% in TEMSR arm, 8% in IFN-α arm, and 16% in combination IFN-α/TEMSR arm), edema (9%, 4%, and 3%), and increased creatinine (14%, 11%, and 20%). Most cases of edema and peripheral edema were of low grade. Only 2.4% and 0.5% of patients in the temsirolimus arm experienced grade 3/4 peripheral edema or edema, respectively. Although increases in creatinine occurred more often in patients receiving temsirolimus than in those receiving IFN-α, acute renal failure was reported less commonly in the temsirolimus alone arm (1.4%) than in the IFN-α arm (3%) or the combination IFN-α/temsirolimus arm (1.9%).

Although approximately half of the renal TEAEs were judged by the investigator to be unrelated to treatment, renal TEAEs that were related to study drug remained much more common among patients receiving temsirolimus. Using the sponsor's determination of causality, increased creatinine due to study drug occurred approximately three times more often in the TEMSR arm (11%) than in the IFN-α arm (4%). Similarly, peripheral edema and edema due to study drug occurred about twice as often in the temsirolimus arm compared with the IFN-α arm.

Although the overall incidence of ARF in the temsirolimus arm was lower than in the IFN arm, there were unusual cases of rapidly progressive ARF, including cases not responsive to hemodialysis, which occurred in patients receiving temsirolimus. See Section 7.1.1 for detailed narratives describing such cases.

7.3.6 Infection-Related Events

Infectious events were increased among patients receiving temsirolimus either alone or in combination. Infections not otherwise specified (NOS) were the most commonly reported infectious event and were increased approximately three-fold in the temsirolimus arm and the IFN-α/temsirolimus arm (14% for both) compared with the IFN-α arm (5%). The most commonly identified site of infections was the respiratory tract (pneumonia or bronchitis). While the incidence of bronchitis was similar among the treatment arms (3.8% in the temsirolimus or IFN-α/temsirolimus arms versus 3.0% in the IFN-α arm), pneumonia was reported approximately twice as often in patients receiving temsirolimus (7.2% for TEMSR, 4.0% for IFN-α, and 8.7% for IFN-α/TEMSR).

Although the majority of infectious TEAEs were judged by the sponsor to be unrelated to treatment, both drug-related infections in general and pneumonia in particular continued to be observed more commonly in patients receiving temsirolimus than in those receiving IFN-α. Drug-related infection NOS occurred in 3.8% of patients in the temsirolimus arm and 1% in the IFN-α arm, and drug-related pneumonia occurred 1.9% of patients in the temsirolimus arm versus 0% in IFN-α arm.

The incidence of neutropenia was lower in patients receiving temsirolimus (7%) compared to those receiving IFN-α (13%). Also of note, despite the increased incidence of lymphopenia in patients receiving temsirolimus, no systemic fungal or pneumocystis carinii infections were reported in these patients.

Reviewer Comment: The incidence of infectious events was higher in patients who received temsirolimus. The most commonly involved organ system was respiratory. It is surprising given the relationship of temsirolimus to sirolimus, as well as the high incidence of lymphopenia in patients taking temsirolimus, that no systemic fungal or pneumocystis infections have been reported.

7.3.7 Pulmonary Events

Interstitial lung disease (ILD) has been reported in association with temsirolimus use. In Study 3066-K1-304WW, there were five cases (2.4%) of ILD (coded as pneumonitis or alveolitis) in the temsirolimus arm compared with one case in the IFN-α arm (0.5%) and one case (termed bronchiolitis) in the IFN-α/temsirolimus arm (0.4%), all but one of which were judged at least possibly related to treatment. The cases in patients who received temsirolimus, either alone or in combination with IFN-α, occurred predominantly in males (5 out of 6 cases), generally reflecting the demographics of the underlying patient population. Half of the patients were under age 65, and half were over age 65. There was no clear trend of duration of drug exposure and incidence of ILD. There was no clear relationship of drug exposure to onset of ILD. These cases were reported as early as the first day of treatment with temsirolimus and as late as week 41 of treatment. ILD resulted in the deaths of 2 of these patients, 1 in the temsirolimus arm and the other in the IFN-α/ temsirolimus arm.

The five cases of ILD (termed pneumonitis or alveolitis) reported in the temsirolimus arm and one case of ILD (termed bronchiolitis) in the IFN-α/temsirolimus arm are briefly summarized below:

ILD cases in the Temsirolimus 25 mg IV 1x/wk arm:

Patient 045001:

This 70 year old white male received his first dose of temsirolimus on 08/02/2004. He continued temsirolimus weekly for 8 weeks at which time he was diagnosed with grade 2 pneumonitis. The drug was withheld for 2 weeks then reduced to 20 mg. He continued treatment until 11/01/2004 at the reduced dose but ultimately experienced complications of a gastrointestinal bleed due to portal hypertension requiring discontinuation of the drug. He died from progressive renal cell carcinoma on [redacted]

Patient 050002:
This 48 year old white male received his first dose of temsirolimus on 05/17/2004. At baseline, he had a "pleural-based mass, RLL airspace disease, and dyspnea." On [redacted] he experienced right-sided chest pain and dyspnea requiring hospitalization. A chest x-ray on [redacted] showed infiltrates in the left upper lobe which were "likely pneumonia" and a right pleural effusion, as well as a stable right lytic rib lesion. He was diagnosed with pneumonitis that was judged probably related to study drug, and treatment was withheld. He restarted temsirolimus on 03/07/2005, approximately 3 weeks from his last dose, but then withdrew from the study 4 days with the sponsor citing "Reason: Other: does not want any more drug". He was readmitted to the hospital from [redacted] and from [redacted] with pain and shortness of breath attributed to successively higher grades of pneumonitis. He was discharged to his home under hospice care where he died on [redacted] with the cause of death reported as "progressive disease". Of note, a grade 5 AE of pneumonitis is listed on the patient's case report form.

Patient 528006:
This 52 year old Caucasian male received his first dose of temsirolimus on 09/27/2004. At his scheduled visit during week 24 on 03/16/2005, a TEAE of grade 1 pneumonitis (diagnosed by chest radiograph findings) was recorded with a start date of 01/26/2005. The AE was judged probably related to test article by the investigator. The temsirolimus was continued, and no medications were recorded as having been given to treat the pneumonitis. Grade 1 pneumonitis was still present in 06/2005 at the time of his study withdrawal due to disease progression. There were no other pulmonary AEs recorded for him. He was still alive as of the data lock date of 05/30/2006.

Patient 557001:
This 53 year old Caucasian female received her first dose of temsirolimus on 08/06/2004. At her scheduled visit during week 4 on 08/31/2004, a TEAE of grade 2 "alveolitis" (verbatim term and preferred term) was recorded with a start date of 08/26/2004 and a stop date of 08/31/2004. No other details are available as to how this diagnosis was made, and the AE was judged definitely not related to treatment by the investigator. Temsirolimus was withheld on 08/26/2004 due to this AE. Ultimately, the patient continued to receive temsirolimus until 05/2005 when she experienced disease progression. There were no other pulmonary AEs recorded for her. She was still alive as of the data lock date of 05/30/2006.

Patient 813003:
This 69 year old Asian male received his first dose of temsirolimus on 02/10/2004. His temsirolimus was withheld for one week then reduced in dose due to thrombocytopenia. He

continued to receive temsirolimus at the reduced dose of 20 mg IV weekly until 03/29/2004 (week 8). At week 9, he was found to have progressive disease and received no further treatment with temsirolimus. He reported grade 1 dyspnea judged possibly related to temsirolimus on 04/02/2004. On 04/05/2004, he was diagnosed with grade 2 pneumonitis, with a chest x-ray on 04/12/2004 showing nodular densities with bilateral interstitial infiltrates involving both lungs. He was treated with IV cefuroxime, isepamicin, penicillin G, ciprofloxacin, and fluconazole. A second AE of pneumonitis, which was grade 3, was recorded on 04/17/2004. A repeat chest x-ray showed no significant change in the infiltrates. He was begun on amphotericin B for 10 days followed by oral fluconazole at the time of hospital discharge on [redacted] The end date of the pneumonitis AE is listed as [redacted] although no information is available from the sponsor as to the patient's subsequent pulmonary status. He died on [redacted] after receiving several other anti-cancer therapies with his cause of death reported as respiratory failure due to progressive renal cell carcinoma.

ILD case in the Temsirolimus 15 mg IV 1x/wk and IFN-α 6 MU SQ 3x/wk arm:

Patient 575001:
This 69-year-old white man, assigned to the combined IFN-α/temsirolimus arm, began IFN-α on 08/06/2004. He was hospitalized with acute onset of dyspnea 24 hours after receiving his first and only dose of temsirolimus on [redacted] He was treated with oxygen, acetylcysteine, IV furosemide, IV cefotaxime, IV erythromycin, IV dexamethasone, and ipratropium. His respiratory insufficiency improved briefly on an increased dose of dexamethasone, but then worsened again, and he died on [redacted] 10 days after his only dose of temsirolimus. An autopsy demonstrated within the lungs signs of fulminant retro-obstructive bronchopneumonia, focal signs of cavitation, and necrosis. The family did not provide consent for microscopic postmortem examination. The cause of death was reported as bronchiolitis obliterans probably related to test article according to the investigator.

Given the considerable clinical challenges of diagnosing ILD both in general and particularly in an advanced cancer population, an analysis was performed by this reviewer using adverse events that could be representative of ILD without having been recognized or coded as such. Overall, 41% of patients in the temsirolimus arm experienced any pulmonary TEAE compared with 33% in the IFN-α arm. In addition to a diagnosis of ILD itself, the following pulmonary AEs occurred more commonly among patients exposed to temsirolimus, either alone or in combination with IFN-α, than to those who were not exposed to the drug: dyspnea, increased cough, pneumonia, upper respiratory infection, pulmonary physical finding, and wheezing. These findings are shown in the table below and suggest the need for increased vigilance in identifying cases of ILD as larger numbers of patients are exposed to temsirolimus in the post-marketing period.

Table 7.17 Incidence of Pulmonary Adverse Events that Could Represent ILD

ADVERSE EVENT	TEMSR		IFN-α		IFN-α/TEMSR	
	N	%	N	%	N	%
Dyspnea	57	27.4	43	21.5	51	24.5
Cough Increased	53	25.5	29	14.5	48	23.1
Pneumonia	15	7.2	8	4.0	15	7.2
Upper Respiratory Infection	14	6.7	1	0.5	6	2.9
Pulmonary Physical Finding	10	4.8	3	1.5	6	2.9
Wheezing	3	1.4	2	1.0	2	1.0
Pneumonitis	4	1.9	1	0.5	0	0.0
Alveolitis	1	0.5	0	0	0	0
Bronchiolitis	0	0	0	0	1	0.5

Datasets: ADVERSE.xpt and BASELINE.xpt

In addition to the cases of ILD diagnosed in Study 3066K1-304-WW, a total of 7 other patients with an AE of ILD were identified in the phase 1 and 2 studies of temsirolimus. Brief narratives compiled by this reviewer appear below:

Study 3066K1-101-EU: Temsirolimus 220 mg/m^2 IV weekly

- Patient 843/016 was a 56 year old man with metastatic RCC. He developed severe respiratory distress during week [redacted] of treatment. He was withdrawn from the study, hospitalized, and treated with antibiotics, steroids, and diuretics. Imaging one week later showed "clear progression of a bilateral interstitial diffuse pneumopathy". He died [redacted] days after symptom onset. His autopsy reported "very marked diffuse pulmonary parenchymatous alveolitis-like lesions and fibrosis of the alveolar walls, with desquamation of the bronchial epithelium. The cause of death was "attributable to pulmonary parenchyma changes which did not appear to be secondary to an infection, but could have been side effects of chemotherapy with CCI-779."

Study 3066K1-103-EU: Temsirolimus 45 mg/m^2 IV weekly + 5-FU 2600 mg/m^2 + Leucovorin 200 mg/m^2

- Patient 883/21 was a 67 year old man with metastatic adenocarcinoma of the gall bladder. He first developed grade 1 dyspnea during week 5 of treatment. The study drugs were continued, with progressive dyspnea. At week 8, he was noted to have fever, grade 4

dyspnea, and grade 3 hypoxemia. Imaging of the lungs showed changes consistent with probable drug-induced alveolitis. He withdrew from the study due to the event, was treated with antibiotics, steroids, and oxygen, and had recovered approximately 4 weeks later.

Study 3066K1-200US: Temsirolimus 75 mg IV weekly

- Patient 304 was a 63 year old man with metastatic RCC. He developed dyspnea and bilateral pulmonary infiltrates during week 25 of treatment. He was treated with steroids, which provided partial relief of his symptoms, and withdrew from the study 5 weeks later due to pneumonitis. He died [redacted] months after study withdrawal due to progressive renal cell carcinoma.

- Patient 412 was a 75 year old man with metastatic RCC. He developed cough, dyspnea, and pulmonary infiltrates during week 16 of treatment. A lung biopsy was performed which showed pneumonitis with no evidence of an infectious etiology. He discontinued temsirolimus, and his infiltrates improved somewhat over the next 3 weeks, though the AE of pneumonitis was reported as not resolved at the time of study withdrawal.

- Patient 604 was a 57 year old man with metastatic RCC. During week 30 of treatment, he developed bilateral rales and extensive bibasilar infiltrates that failed to improve with antibiotics. A bronchoscopy was negative for any infectious etiology, and a lung biopsy showed hypersensitivity pneumonitis. He discontinued temsirolimus and started on high-dose steroids approximately 1 month later. Imaging 3 months after discontinuing temsirolimus showed resolution of infiltrates, and he was restarted on the drug approximately 5 months after he had discontinued it with no further pulmonary AEs reported.

- Patient 623 was a 58 year old man with metastatic RCC. He was diagnosed with interstitial pneumonitis during week 18 of treatment. He discontinued the drug and was started on steroids. He was rechallenged approximately 4 months after he had discontinued the drug and experienced immediate recurrence of infiltrates. He discontinued the drug after that single dose, and his pneumonitis was reported as not resolved at the time of study withdrawal.

Study 3066K1-203-EU: Temsirolimus 75 mg IV weekly

- Patient 304 was a 46 year old woman with metastatic breast cancer who developed fever, cough, and fibrotic pulmonary changes on imaging during week 8 of treatment. A lung biopsy showed fibrosis with eosinophilic infiltrates. She discontinued the drug and received steroids with clinical improvement. Imaging 6 weeks later showed resolution of the infiltrates.

Reviewer Comment: A total of 13 cases of diagnosed interstitial lung disease (ILD), 3 of which were fatal, have been identified over the entire safety database. Some patients presented with cough, dyspnea, fever, and hypoxia, whereas others were asymptomatic but had radiographic and/or pathologic findings consistent with the diagnosis. There were no demographic or other factors that identified patients at increased risk of ILD, and there was no clear trend of duration of drug exposure and incidence of ILD. The prognosis also varied widely. With discontinuation of temsirolimus and aggressive supportive care, some patients experienced rapidly progressive respiratory failure and death, whereas other patients improved or even had complete resolution, some despite continuation of temsirolimus. Four of the 13 patients were rechallenged, of whom 2 received temsirolimus with no recurrence of symptoms and 2 experienced rapid recurrence of symptoms. Given the increased incidence of unexplained pulmonary TEAEs in the temsirolimus-containing arms and the considerable clinical challenges of making a diagnosis of ILD, especially in an advanced cancer population, it is likely that the true incidence of ILD is higher than is currently known.

7.3.8 Cardiovascular Events

Cardiovascular TEAEs occurred more commonly among patients who received temsirolimus alone (45.2%) or in combination with IFN-α (46.2%) than among patients receiving IFN-α alone (41.5%). Cardiovascular TEAEs that occurred in 5% or more of patients in the temsirolimus arm included: chest pain (temsirolimus 16.3%, IFN-α 9.0%), dizziness (temsirolimus 9.1%, IFN-α 12.5%), hypokalemia (temsirolimus 9.1%, IFN-α 3.5%), hypertension (temsirolimus 6.7%, 3.5%), and somnolence (temsirolimus 6.7%, IFN-α 10.5%). In addition, substernal chest pain was reported in 1.9% of patients in the temsirolimus arm and 1.4% of patients in the combination arm, compared with 0% in the IFN-α arm.

Despite this, the incidence of myocardial ischemia and myocardial infarction was low and did not differ between the temsirolimus and IFN-α arms. Four patients had arrhythmia, one of whom was in the combination arm (grade 2 atrial fibrillation), and the remainder of whom were in the IFN-α arm. No patients in the temsirolimus alone arm experienced arrhythmia. There were no reports of torsade de pointes.

7.3.9 Allergic Reactions

Allergic reactions occurred more commonly among patients who received temsirolimus alone (8.7%) or in combination with IFN-α (5.8%) than among patients receiving IFN-α alone (0.5%).

In the temsirolimus arm, 3 of the 15 patients' allergic reactions were related to exposures other than temsirolimus (iodine or contrast dye). The remaining 12 patients experienced a total of 36 reported allergic reactions, which are discussed in further detail below. All of these were coded grade 1 or 2, although at least one reaction described in detail in the CRF appears to have been more severe. Patient #016005 experienced a reaction of "lightheadedness, eyes rolled back, oral frothing, unresponsive, and blood pressure (systolic) > 190". The other allergic reactions manifested variably as rash, cough, throat/tongue swelling, flushing, and facial numbness. Seven of the 12 patients (58%) had allergic reactions reported with subsequent temsirolimus exposure, whereas the remaining 5 patients (42%) did not. In 33% of reported reactions, no action was taken. In 22% of reported reactions, the temsirolimus infusion was temporarily discontinued. In 67% of reported reactions, patients were treated with an antihistamine, H2 blocker, steroid, or a combination of these medications. No patients in the temsirolimus arm required emergency room visits or hospitalization due to allergic reactions.

In the combination arm, of the 12 patients who experienced allergic reactions, 10 appeared to be related to study drug. Two of these patients had grade 3 allergic reactions, and 1 had a grade 4 allergic reaction. The manifestations of allergic reaction in this group were also varied but, in some cases, included more serious symptoms such as hypertension, chest pain, severe dyspnea, cyanosis, and decreased level of consciousness. The patient with a grade 4 allergic reaction experienced this in week 8 of treatment with no prior reported allergic reactions. Despite discontinuation of the infusion and supportive treatment, this patient required hospitalization and withdrew from the trial.

Following an initial allergic reaction, many patients were given more aggressive premedication prior to subsequent infusions of temsirolimus, including antihistamines, H2 blockers, and steroids. More extensive premedication appeared to prevent some, but not all, future allergic reactions.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. See Section 7.1.

7.4.1.1 Pooled data vs. individual study data

Not applicable. See Section 7.1.

7.4.1.2 Combining data

Not applicable. See Section 7.1.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Explorations for dose dependency are confounded by the fact that patients receiving the lower dose of temsirolimus (15 mg IV weekly) received the drug in combination with various doses of IFN-α, whereas patients receiving the higher dose of temsirolimus (25 mg IV weekly) received the drug alone. Adverse events generally occurred much more frequently for patients assigned to the combination arm.

See also Section 7.1.7.

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.1.1 Hyperglycemia and diabetes mellitus

Adverse events related to hyperglycemia were more than twice as common in patients receiving temsirolimus monotherapy than in those receiving IFN-α alone (TEMSR 26%, IFN-α 11%). In the temsirolimus arm, TEAEs related to new hyperglycemia or significant worsening of existing hyperglycemia were reported as early as two days after beginning study drug and as late as 252 days after beginning study drug. The median number of days from initiation of temsirolimus to a TEAE of hyperglycemia was 27 days, and the mean was 40 days. The sponsor did not require data collection on concomitant medications or laboratories following discontinuation of study drug, and thus the reversibility of hyperglycemia following discontinuation of temsirolimus could not be assessed.

7.4.2.1.2 Hyperlipemia and hypercholesterolemia

Adverse events related to hypercholesterolemia and hyperlipemia were also much more common among patients receiving temsirolimus monotherapy (25% and 27%, respectively) than in those receiving IFN-α alone (5% and 14%, respectively). In the temsirolimus arm, AEs related to newly elevated serum lipids or worsening of existing abnormalities in lipid profile were reported as early as one day and as late as 336 days after beginning study drug. The mean number of days from initiation of temsirolimus to a TEAE related to lipid abnormalities was 15 days, and the mean was 32 days. The sponsor did not require data collection on concomitant medications or laboratories following discontinuation of study drug, and thus the reversibility of abnormalities in lipid profile following discontinuation of temsirolimus could not be assessed.

7.4.2.1.3 Rashes

Rashes were also much more common among patients in the temsirolimus arm (37% for rash not otherwise specified and 57% for rash of any description) than in the IFN-α arm (6% for rash not otherwise specified and 15% for rash of any description). In the temsirolimus arm, adverse events involving rash, defined as rash of any description including exfoliative dermatitis, were observed as early as 2 days and as late as 340 days after initiation of study drug. The mean number of days from initiation of temsirolimus to development of a rash was 17 days, and the mean was 34 days.

In addition, please refer to Section 7.3.7 for a detailed discussion of interstitial lung disease (ILD).

7.4.2.3 Explorations for drug-demographic interactions

From the sponsor:
"The incidence of TEAEs was analyzed by age (<65 years vs. >65 years) and sex (men vs. women) for 208 patients who received temsirolimus 25 mg in the phase 3 advanced RCC study (3066K1-304-WW). Subgroup analysis of TEAEs by race was not informative because most patients (185, 89%) in the study were Caucasian."

"In the temsirolimus 25-mg group, 145 (70%) patients were <65 years old and 63 (30%) patients were >65 years old. The incidence of TEAEs was generally similar for patients <65 years old and patients >65 years old. TEAEs with at least twice the incidence in older patients as in younger patients in the temsirolimus arm (and were reported for at least 10% of patients in either age group) and did not also have twice the incidence in older patient in the IFN-α arm were: face edema, diarrhea, lactic dehydrogenase increased, and pneumonia. Of these TEAEs, diarrhea had higher incidence in older than younger patients in the IFN-α arm (diarrhea: 28.6% and 16.1% for older and younger patients, respectively). Thus, older patients treated with temsirolimus appear to have an increased incidence of face edema, lactic dehydrogenase increased, and pneumonia compared with younger patients."

"In the temsirolimus 25-mg group, 138 (66%) patients were men and 70 (34%) patients were women. The incidence of most TEAEs was generally similar for men and women. While there were a number of events that had at least twice the incidence in patients of one sex versus patients of the other sex in the temsirolimus arm, these events were disparate in nature. There were no consistent trends indicating increased risk for any event based on sex."

7.4.2.4 Explorations for drug-disease interactions

All of the patients in Study 3066K1-304-WW had advanced RCC. The most common histologic subtype (>80% in all arms) was clear cell carcinoma, which is representative of histology in the general population of RCC patients. Other histologies were not represented in significantly large numbers to permit meaningful analysis of drug-disease interactions by histologic subtype of disease.

7.4.2.5 Explorations for drug-drug interactions

From the sponsor:

"Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus Cmax (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus Cmax by 65% and AUC by 56%, and AUCsum (composite of temsirolimus AUC plus sirolimus AUC) by 41% compared to TORISEL treatment alone. Therefore, concomitant treatment with agents that have CYP3A4/5 induction potential should be avoided. If alternative treatment cannot be administered, a weekly intravenous dose of TORISEL up to 50 mg should be considered."

"Co-administration of TORISEL with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus Cmax or AUC; however, sirolimus AUC increased 3.1-fold, and AUCsum increased 2.3-fold compared to TORISEL alone. Substances that are potent inhibitors of CYP3A4 activity increase sirolimus blood concentrations. Concomitant treatment of TORISEL with agents that have strong CYP3A4 inhibition potential should be avoided."

"In 23 healthy subjects, the concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of TORISEL was co-administered. No clinically significant effect is anticipated when temsirolimus is co-administered with agents that are metabolized by CYP2D6."

7.4.3 Causality Determination

See Section 7.3.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dose and schedule for temsirolimus in advanced RCC is 25mg IV over 30-60 minutes once weekly after pre-medication with antihistamines. Dose reductions to 20 mg or 15 mg can be considered in the setting of intolerable toxicity.

8.2 Drug-Drug Interactions

8.2.1 CYP 3A4 Inhibitors

Dose of temsirolimus should be decreased to 12.5 mg IV weekly if concomitant CYP 3A4 inhibitors must be used.

8.2.2 CYP 3A4 Inducers

Dose of temsirolimus should be increased to 50 mg IV weekly if concomitant CYP 3A4 inducers must be used.

Temsirolimus is not a CYP2D6 or CYP3A4 inhibitor.

8.3 Special Populations

Hepatic Impairment
A hepatic impairment study is ongoing at the time of this review. Wyeth has indicated that the hepatic impairment study has a projected completion date of 3Q2007.

Pediatrics
A phase 2 pediatric study (n=20) is ongoing. [redacted] Wyeth was advised by the FDA that in addition to study reports, raw data for PK and clinical studies should be submitted in order fulfill the requirements for a pediatric exclusivity extension under section 505A of the Best Pharmaceuticals for Children Act.

8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this application.

8.6 Literature Review

A literature review was performed on the natural history of renal cell carcinoma, available treatments for RCC, published efficacy trials for RCC, and any studies published using temsirolimus. No additional information regarding the efficacy or safety of temsirolimus was obtained via literature review.

8.7 Postmarketing Risk Management Plan

There are no postmarketing risk management plans in place at this time.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The trial supporting approval of temsirolimus is a randomized, open label, active comparator arm trial using IFN-α, temsirolimus, and a combination group receiving both agents. The population was treatment naïve patients with a poor prognosis (meeting a pre-specified set of prognostic factors).
Group treatment assignments were as follows (stratified by region and nephrectomy status):
--Temsirolimus 25 mg IV weekly (n=209)
-- IFN-α subcutaneously three times weekly (n=207)
--Temsirolimus 15 mg IV weekly + IFN-α subcutaneously three times weekly (n=210)

Six-hundred and twenty-six patients were randomized to the study in a 1:1:1 ratio. The three treatment arms were well balanced for the demographic characteristics of race, gender, and age.

For the analysis of overall survival in the ITT population, there were 446 death events (72% of the interferon group, 68.4% of the temsirolimus group, and 73.3% of the IFN-α/temsirolimus group). This analysis was the second interim analysis for the trial. It was not pre-specified in the original protocol but was agreed upon by the FDA after the initial interim analysis failed to cross the O'Brien-Fleming boundary for superior efficacy for the comparison of the temsirolimus and IFN-α groups after 239 events.

A statistically significant and clinically relevant improvement in median overall survival was seen in patients randomized to the temsirolimus arm versus the IFN-α arm. Median overall survival was 10.9 months (95% CI 0.58-0.92) for temsirolimus-treated patients and 7.3 months for IFN-α-treated patients, a difference that was statistically and clinically significant. The hazard ratio for temsirolimus was 0.73 (p=0.0078) and 0.96 for IFN-α/temsirolimus (p=0.6965).

A statistically significant and clinically relevant improvement in median progression-free survival was seen in patients randomized to the temsirolimus arm versus the IFN-α arm. Median progression-free survival was 5.5 months (95% CI 3.9-7.0) for the temsirolimus arm, 4.9 months for the combination arm, and 3.1 months for the interferon arm. The hazard ratio was 0.66 (p=0.0001) for temsirolimus and 0.73 (p=0.004) for the combination group.

Overall responses (per independent radiology assessment) were limited to partial responses. No independent radiologist reviewed complete responses were observed in any treatment arm. The temsirolimus arm achieved an 8.6% ORR and the combination arm achieved an 8.1% ORR compared to a 4.8% ORR in the interferon arm. The differences in overall response were not

statistically significant between treatment arms for either the investigator assessment or the independent assessment.

Based on the independent reviewer assessment of response, the median duration of response was 11.1 months in the temsirolimus arm, 7.4 months in the interferon arm, and 9.1 months in the combination arm. There was no statistically significant difference in duration of response between either temsirolimus-containing arm and interferon alone.

The most common non-laboratory related TEAEs (≥ 30%) in the temsirolimus arm were: rashes, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥ 5%) grade 3 and 4 non-laboratory-related TEAEs in the temsirolimus arm were: asthenia, dyspnea, rash, and pain.

The most common laboratory abnormalities (≥ 30%) in the temsirolimus arm were anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and neutropenia. The most common (≥ 5%) grade 3 and 4 laboratory abnormalities in the temsirolimus arm were: hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.

9.2 Recommendation on Regulatory Action

The clinical reviewers recommend regular marketing approval for temsirolimus as a single agent for the treatment of advanced renal cell carcinoma. This recommendation is based upon a clinically meaningful and statistically robust improvement in overall survival and progression-free survival in patients receiving temsirolimus as first-line treatment of advanced renal cell carcinoma compared to those patients receiving IFN-α with a toxicity profile that is acceptable for this patient population.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Unusual toxicities that are seen with temsirolimus, including interstitial lung disease, dyspnea, hyperglycemia, infections, bowel perforation, acute renal failure, and drug-drug interactions, will be described in the labeling.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

9.3.2 Required Phase 4 Commitments

1) Submit the completed report for the thorough QT prolongation evaluation and datasets for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2- period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects"

Protocol Submission: March 2006
Study Start: March 2006
Final Report Submission: September 2007

2) Submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US))

Protocol Submission: November 2005
Study Start: January 2006
Final Report Submission: September 2008

9.3.3 Other Phase 4 Requests

9.3.3.1 Pediatric Written Request: Wyeth was advised by the FDA [redacted] that in addition to study reports, raw data for PK and clinical studies should be submitted in order fulfill the requirements for a pediatric exclusivity extension under section 505A of the Best Pharmaceuticals for Children Act. The sponsor will continue the study as currently designed.

[redacted]

9.4 Labeling Review

Consultation was requested of the Division of Medication Errors and Technical Support (DMETS). No concerns were raised regarding the trade name "Torisel". Concerns were raised regarding the potential for overdose if the entire contents of the admixed vial (containing diluent and temsirolimus) were administered. This vial contains overfill and the Applicant's proposed label does not indicate this. In addition, the proposed label does not clearly state that the final concentration of the admixture of diluent plus temsirolimus is actually 10 mg/ml. The current proposed vial label indicates a strength of 25 mg/ml temsirolimus. Changes are proposed to the vial labels. Agreement on final labeling is pending.

The Applicant has not provided a proposed Medication Guide or Patient Package Insert. It is recommended that the Applicant propose such document and submit for review to DDMAC.

9.5 Comments to Applicant

None.

10 APPENDICES

10.1 Review of Individual Study Reports

Two trials were submitted for demonstration of clinical efficacy and safety. They are

- 3066K1-200-US A Randomized, double-blind, phase 2 study of intravenous CCI-779 (temsirolimus) administered weekly to patients with advanced renal cell carcinoma.
- 3066K1-304-WW A Phase 3, three-arm, open-label study of interferon alfa alone, CCI-779 alone, and the combination of interferon and CCI-779 in first-line poor-prognosis subjects with advanced renal cell carcinoma.

The phase 3 study is acceptable as a registration study and has been reviewed in Section 6.0 of this report. Study 200 is not acceptable as a registration study because it is an uncontrolled study performed for dose-finding purposes. Study 200 does provide safety data and has been reviewed in detail below.

10.1.1 Protocol

Protocol 3066K1-200-US: A Randomized, Double-Blind, Phase II Study of Intravenous CCI-779 Administered Weekly to Patients with Advanced Renal Cell Carcinoma

Trial 3066K1-200-US is a well-designed, randomized, double-blind, multi-center phase 2 study of three different dose levels of intravenous temsirolimus in patients with advanced RCC (renal cell carcinoma). The pharmacists and pharmacokineticists were unblinded to the patient dose. Eligible patients were randomized to receive 25 mg, 75 mg, or 250 mg of temsirolimus weekly until evidence of disease progression.

One hundred eleven (111) patients were enrolled in the study, and the primary analysis was based upon the ITT population and the evaluable population. To be evaluable for tumor response, a patient must have received at least 8 weekly doses of temsirolimus and had at least one tumor measurement, unless the patient discontinued because of disease progression or adverse events.

The primary objective was to evaluate the safety and efficacy of 3 dose levels of temsirolimus when administered to previously treated patients with advanced RCC or to previously untreated patients who were not appropriate candidates for high-dose IL-2 therapy. The secondary objectives were to assess the PK parameters of temsirolimus and, as appropriate, evaluate a possible pharmacodynamic relationship with clinical response.

CCI-779 will be administered weekly as a 30-minute infusion 30 minutes after pre-medication with IV diphenhydramine 25-50 mg. Hypersensitivity reactions will be treated by stopping the infusion, repeat administration of a histamine H2-receptor antagonist, and/or slowing the rate of the infusion.

The National Cancer Institute Common Toxicity Criteria Scale, version 2 (copies will be provided to the sites), will be used to grade toxicities. Investigators should make an immediate effort to determine the etiology of the clinical or laboratory abnormality. If a patient experiences a toxicity determined to be at least possibly related to CCI-779 administration, the dose administered for subsequent weeks may require a reduction of the dose, depending on the grade and type of toxicity observed.

Table 10.1 Protocol Dose Modification Plan for Hematologic Parameters

Dose Modifications Based on Weekly ANC and Platelet Counts

ANC (/μL)	Platelets (/μL)	% of Planned CCI-779 Dose
≥ 1000	and ≥ 80,000	100%
750-999	or 50,000 to < 80,000	hold*
< 750	or < 50,000	hold**

* Upon recovery to ANC ≥ 1,000/μL and platelets to ≥ 80,000/μL, 75% of dose will be administered.
** Upon recovery to ANC ≥ 1,000/μL and platelets to ≥ 80,000/μL, 50% of dose will be administered.

Table 10.2 Protocol Dose Modification Plan for Non-Hematologic Parameters

Dose Modifications Based on CCI-779-Related Non- Hematologic Toxicities

NCI Grade	% of Planned CCI-779 Dose
0-2+	100%+
3*	hold**
4	hold***

\+ For symptomatic Grade 2 toxicity, the dose may be held until recovery to CTC Grade 0-1, then 75% of the dose administered, at the investigator's discretion.
* Except nausea/vomiting (unless patients are on optimal antiemetic therapy)
** Hold until recovery to CTC Grade 0-2 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), then 75% of dose will be administered.
*** Hold until recovery to CTC Grade 0-2 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), then 50% of dose will be administered.

For any toxicities not covered by the above guidelines, the value must return to the eligibility criteria specified in Section 7 or be discussed with the medical monitor for the patient to continue in the study. The appearance of any other symptoms which, in the opinion of the investigator, are drug-related or hazardous to the patient's well-being, is sufficient justification to modify the dosage or discontinue the drug.

Following dose reduction, if this dose is maintained for 4 weeks without further dose reduction, subsequent dose escalation to prior levels may be considered. Notification of the WR Medical Monitor/Clinical Scientist is required in the event of dose modification or discontinuation. Patients will be allowed two dose reductions. If any patient has further toxicities that would require further reduction, the patient will be discontinued from the study unless the investigator and medical monitor agree that the patient should remain in the study. If treatment is held for more than 2 consecutive weeks, the patient will be removed from the study, unless the investigator and medical monitor agree that the patient should remain in the study.

Patients may remain on study until there is evidence of disease progression, and as long as the treatment is tolerated. For patients whose disease is not progressing after 1 year of treatment, consideration will be given to continuing treatment beyond this time upon review of the patient's safety data and discussion with the medical monitor.

Primary Endpoint: The primary efficacy endpoint of this study is tumor response rate (percentage of patients with complete or partial response [see below]). In addition, the percentage of patients achieving minor response or stable disease will be evaluated. All patients will be evaluated for efficacy by tumor measurements approximately every 12 weeks (Site specific). Responses (for all responding patients) will be confirmed by independent review if sufficient responses are observed.

Secondary Endpoints: The secondary efficacy endpoints will be duration of response, time to response, time to tumor progression, progression-free survival, proportion of patients progression-free at 8 weeks (and possibly other times), patients with progression-free survival at 8 weeks, ECOG performance status, and survival. In addition, an attempt will be made to correlate antitumor responses with the molecular/growth factor or other targets noted in Section 9.1, if appropriate.

Eligibility Criteria:

Inclusion Criteria
1. Patients with histologically confirmed advanced renal cancer who have received prior therapy for advanced disease, or who have not received previous treatment for advanced disease but are not appropriate candidates to receive high dose IL-2 therapy.
2. Bi-dimensionally measurable ($\geq$ 1 cm) evidence of residual, recurrent, or metastatic disease by physical or radiographic examination (metastases only to bone will not be eligible).
3. Patients must have demonstrated progression of their disease (new lesions or an increase in the size of lesions) prior to study entry.

4. Age ≥18 years old.
5. ANC ≥ 1500/μL, platelet count ≥ 100,000/μL, hemoglobin ≥ 8.5 g/dL.
6. Adequate renal function (serum creatinine ≤1.5 x upper limit of normal or calculated creatinine clearance ≥ 60 mL/min).
7. Adequate hepatic function (bilirubin ≤ 1.5 x upper limit of normal, AST ≤ 3 x upper limit of normal [< 5 x upper limit of normal if liver metastases are present]).
8. Serum cholesterol ≤ 350 mg/dL, triglycerides ≤ 300 mg/dL.
9. ECOG performance status 0-1.
10. Life expectancy of at least 12 weeks.
11. Signed and dated consent form.

Exclusion Criteria

1. Known CNS metastases (if previously treated by surgery or radiotherapy and stable for 2 evaluations at least 8 weeks apart at time of study, asymptomatic, and not requiring the use of steroids and anticonvulsants, patient may be entered).
2. Surgery or local radiotherapy within 3 weeks of start of dosing.
3. Chemotherapy or biologic therapy for renal cancer within 4 weeks of start of dosing.
4. Prior investigational agent within 4 weeks of start of dosing.
5. Immunocompromised patients, including patients known to be HIV positive, or concurrent use of immunosuppressive agents, including corticosteroids.
6. Active infection or serious intercurrent illness.
7. Requiring anticonvulsants.
8. Presence of unstable angina, recent myocardial infarction (within the previous 6 months), or use of ongoing maintenance therapy for life-threatening arrhythmia.
9. History of prior malignancy in past 3 years, other than basal cell carcinoma or squamous cell carcinoma of the skin, or if received systemic therapy for prior malignancy.
10. Known hypersensitivity to macrolide antibiotics (e.g. clarithromycin, erythromycin, azithromycin).
11. Pregnant or nursing women, or women of childbearing potential who are not using an effective contraceptive method.
12. Any other major illness which, in the investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.

Expressly Permitted Concomitant Treatment

- Epoetin alfa
- Bisphosphonates

Prohibited Concomitant Treatment

- Chemotherapy other than CCI-779
- Radiation therapy
- Hormonal therapy for underlying malignancy (megestrol acetate is allowed for appetite)
- Other investigational agents
- Systemic corticosteroids and other immunosuppressive therapies

- Anticonvulsants (carbamazepine, phenobarbital, phenytoin)
- Cytochrome P450 inhibitors or inducers
- Drugs that otherwise affect blood levels of sirolimus are to be avoided if possible.
- Prophylactic growth factors to support neutrophils (may be used at discretion of investigator in patients who develop infectious complications)

Baseline Evaluation

- Verification of eligibility criteria
- Medical history
- Complete physical examination with review of systems and vital signs
- ECOG Performance Status
- Chest x-ray if no thoracic CT within 2 weeks of enrollment
- 12-lead ECG
- (within 4 weeks of study start) Tumor Assessment: Head CT, chest CT, abdominal/pelvic CT, and radionuclide bone scans (as clinically indicated)
- Serum VEGF level
- (within 7 days of study start) Laboratory Evaluation—CBC with differential, fasting chemistry panel and electrolytes, coagulation profile, urinalysis, serum pregnancy (for women of childbearing potential)

On-Study Evaluations

- Pharmacokinetics testing on 10 patients during week 1 and week 4
- Tumor measurements (by same technique used at baseline) every 12 weeks. Tumor response determined by the sum of the products of all measurable lesions. Bone lesions are not considered measurable disease.
- Interim physical exam, ECOG, and weight at least every 4 weeks
- Vital signs are to be assessed before each dose of CCI-779, before relevant PK sample times, and before discharge from the study site.
- CBC with differential weekly
- Fasting chemistry panel/electrolytes every 2 weeks
- Coagulation panel every 4 weeks
- Serum VEGF level every 8 weeks
- Blood samples for PBMC analysis at 8 and 16 weeks if pharmacogenomics/special testing/future research consent is signed
- Full pharmacokinetic profiles for CCI-779 and sirolimus from approximately 10 patients during the 1st and 4th weekly CCI-779 administrations. Sample times are pre- dose, 0.5 hours, 1, 2, 6, 24, 72, 96, and 168 hours after start of infusion.
- Whole blood to assess CCI-779 plasma levels will be obtained at pre-dose timepoint and at 0.5 and 6 hours following administration (prior to the 4th weekly dose, immediately after infusion of the 4th dose, and on one other day during the week following the 4th dose, if possible.
- Monitor adverse events--continuously

Final Evaluation

- Complete physical examination
- ECOG
- Vital signs
- ECG
- Laboratories: CBC with diff, urinalysis, fasting chemistry panel and electrolytes, coagulation tests
- Adverse event assessment
- If patient goes off study for progressive disease, a blood sample for PBMC analysis will also be obtained.
- Patients with no evidence of drug-related toxicity at final visit will be followed for approximately 30 days after the last dose of CCI-779. Patients with evidence of toxicity at final visit will be followed weekly until the toxicity has resolved.
- All patients will be followed approximately every 3 months for survival information and serious adverse events that the investigator thinks may be related to CCI-779.

Table 10.3 Study Schedule

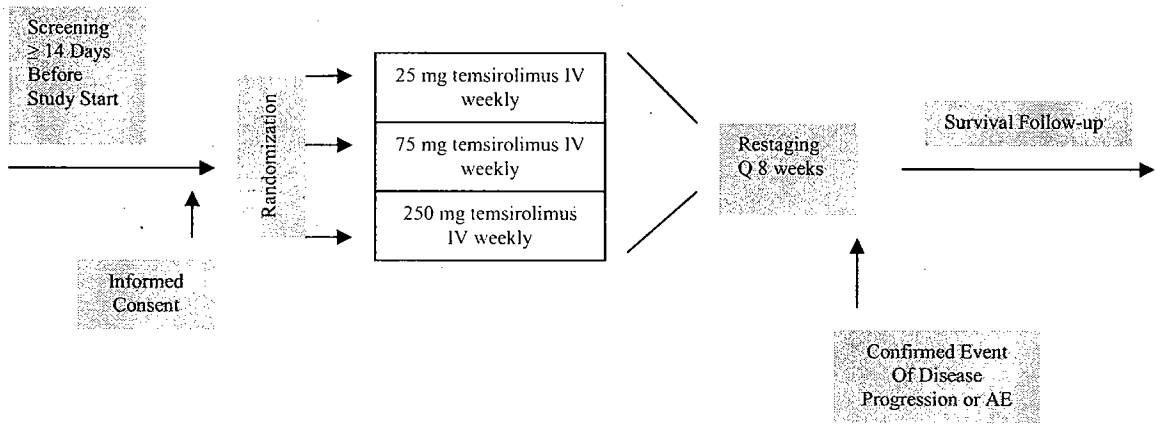
STUDY FLOW CHART

	Prestudy[a] Screening/ Baseline	Each Cycle of Therapy				Final Visit	Follow-Up Period
Day of Cycle[m]		D1	D8	D15	D22		
Medical History	X						
Complete Physical Exam	X					X	
Interim Physical Exam		X[j]					
ECOG Performance Status	X	X[j]				X	
Vital Signs[f]	X	X	X	X	X	X	
Tumor Assessments[b]	X[b]	X[b]				X	
Tumor tissue[k]	X						
Serum VEGF[l]	X	X[l]					
Additional Whole Blood Sample[n]	X						
PBMC Samples[o]	X	X[o]				X[o]	
Chest X-ray	X[c]						
ECG	X					X	
Urinalysis	X[d]					X	
Serum β-HCG	X[g]						
CBC w/differential	X[h]	X[h]	X[h]	X[h]	X[h]	X	
Fasting chem panel/electrolytes	X[h]	X[h]		X[h]		X	
Coagulation profile	X[h]	X[h]				X	
Survival[i]							X[i]
CCI-779 Administration[e]		X	X	X	X		
Pharmacokinetics[f]	See accompanying Pharmacokinetic Flow Chart						
Monitor adverse events	continuously						

a Prestudy screening/baseline evaluation must be done within 2 weeks of the study start, unless otherwise indicated.
b Scans for initial tumor assessment may be done within 4 weeks of study start. During the study, scans for tumor assessments will be made approximately every 12 weeks (Site specific).
c Chest X-ray will be done within 2 weeks of study start, but is not required if patient has had a thoracic CT scan within 2 weeks of CCI-779 administration.
d Tests must be done within 7 days of CCI-779 administration.
e CCI-779 will be administered as a 30 minute IV infusion weekly.
f See Pharmacokinetics Flow Chart for timing of PK assessments and vital signs (for patients who will undergo PK sampling). Vital signs also will be assessed prior to dosing and prior to discharge.
g Obtain serum β-HCG (if appropriate) at baseline. Must be obtained within 7 days prior of CCI-779 administration.
h Tests must be done within 72 hours prior to CCI-779 administration, unless discussed with Medical Monitor (for Baseline, must be done within 7 days of CCI-779 administration).
i Patients will be followed for survival approximately every 3 months following their completion of the study. This contact may be by phone.
j Prior to CCI-779 administration.

k If available, pre-treatment tissue blocks for assessment of PTEN, cyclin D_1, p27 expression, and possibly other targets. In addition, immunohistochemistry testing for Akt phosphorylation and PTEN may be performed at the study sites.
l Serum VEGF levels will be assessed at baseline and at approximately 8 weeks.
m A cycle is defined as 4 weekly doses of CCI-779.
n For possible future analysis
o PBMC blood samples will be obtained at baseline, approximately 8 weeks and 16 weeks, and at time of disease progression.

Figure 10.1 Schema of Study Design (Reviewer's Figure)



Definitions:

Measurable Disease: Bi-dimensionally measurable lesions with both diameters = 1.0 cm by CT scan, X-ray or palpation. All patients on this study must have at least one measurable lesion meeting these criteria.

Evaluable Disease: Uni-dimensionally measurable lesions or lesions with either diameter

Safety population: Patients who receive at least one dose of study drug.

Efficacy population: Patients who receive at least eight weekly doses of CCI-779, unless they discontinued because of disease progression or adverse events.

Complete Response (CR): The disappearance of all known disease, determined by two observations not less than 4 weeks apart.

Partial Response (PR): Fifty percent (50%) or greater decrease in the sum of the products of the perpendicular diameters of all measured lesions, determined by two observations not less than 4 weeks apart. In addition, there can be no appearance of new lesions or progression of any lesion.

Minor Response (MR): Twenty-five percent (25%) or greater decrease but less than 50% decrease from baseline in the sum of the products of the perpendicular diameters of all measured lesions without the appearance of any new lesions.

Stable Disease (SD): Less than a 25% increase or 25% decrease from baseline in the sum of the products of the perpendicular diameters of all measured lesions without the appearance of any new lesions.

Progressive Disease (PD): Any increase of = 25% in the size of one or more measurable lesions or the appearance of new lesions. The data base will reflect this information and the data will be analyzed utilizing this definition. The data will also be analyzed utilizing the following definition of PD: An increase of = 25% in the sum of products or the appearance of new lesions. In addition, the data will be analyzed utilizing a third definition of PD: An increase of = 25% in the sum of products, or an increase of = 50% in a single lesion on sequential measurements, or an increase of = 50% in more than one lesion at one assessment.

Overall Response Rate: The objective response rate is the percentage of patients with a complete or partial response documented on at least two occasions, 4 weeks or more apart. In addition, the percentage of patients achieving minor response or stable disease will be evaluated, and a "response rate" including these patients will be calculated.

Time to Response: Interval from date of initiating CCI-779 treatment until the first date of documentation of partial or complete response.

Duration of Response: Response duration is the interval from the first day of initial documentation of partial or complete response until the first day of measurement of progressive disease, the date of death or censored at the last date of measurement in a patient who is lost to follow-up while in response. This parameter applies to responding patients, and will be analyzed separately for groups with complete remission or partial remission. [In addition to duration of response, duration of minor response or stable disease may be analyzed also.]

Time to Progression: Time to tumor progression is the interval from the date of initial CCI- 779 treatment until the first day of measurement of progressive disease.

Progression-Free Survival: Progression-free survival is the interval from the date of initial CCI-779 treatment until the first day of measurement of progressive disease or death.

Survival: Survival is measured from the date of initial CCI-779 treatment to the time of death, or censored at the last date known alive.

Statistical Analysis Plan

The number of patients chosen was based mainly on clinical considerations. With a sample size of 30 patients, the maximal confidence width of a 95% confidence interval is achieved if 50%, or 15 of the 30 patients, respond; the 95% confidence interval would be 31.3% to 68.7%. If 5 out of 30 patients respond, an observed response rate of approximately 16.7%, the 95% confidence interval would be 5.6% to 34.7%. If the true response rate is 15%, the probability that the 95% confidence interval will not include the spontaneous remission rate of 0.8% will be approximately 0.95.

The primary analysis of the tumor response rate will be the calculation of a 95% exact confidence interval based on the intent-to-treat population, defined as all randomized patients and modified intent-to-treat population, defined as above. A 95% confidence interval of the rate of response also will be calculated for all evaluable patients. Appropriate secondary endpoints may be summarized by the Kaplan-Meier method and other methods, as appropriate. Adverse experience and laboratory test results will be summarized using descriptive statistics.

Reviewer Comments: The statistical plan did not correct α for multiple comparisons, therefore the statistical significance for secondary endpoints is not known.

Eleven (11) patients failed to meet eligibility criteria. Of these, 7 patients were granted an eligibility exemption and all received temsirolimus.

Table 10.4 Summary of Important Protocol Deviations (per Applicant)

Category[a]	No. of Patients	Patient Number(s)
Eligibility criteria violation	11	103, 125, 204, 206, 209, 211, 212, 401, 409, 514, 601
Did not have bidimensionally measurable (≥1 cm) disease	3	209, 212, 601
Did not demonstrate disease progression	2	212, 601
Age not ≥18 years	1	125
Hemoglobin not ≥8.5 mg/dL	1	409
Serum cholesterol not ≤350 mg/dL or triglycerides not ≤300 mg/dL	3	206, 211, 401
Had known CNS metastases	1	204
Received prior investigational agent within 4 weeks of starting dose	1	103
Had prior malignancy in past 3 years, or received systemic therapy for prior malignancy	2	206, 514
Tumor assessments not done	41	101, 102, 106, 114, 116, 118, 119, 127, 129, 132, 133, 203, 204, 205, 206, 207, 209, 210, 211, 212, 401, 402, 403, 404, 406, 407, 409, 411, 414, 501, 508, 603, 604, 606, 608, 612, 618, 619, 621, 624, 626
Target tumors	38	101, 102, 106, 114, 116, 118, 119, 127, 129, 132, 133, 203, 204, 205, 206, 207, 209, 210, 211, 401, 402, 403, 404, 406, 407, 409, 411, 414, 501, 508, 603, 604, 606, 608, 612, 618, 619, 621
At final visit	28	101, 114, 116, 118, 119, 127, 129, 132, 133, 204, 207, 211, 401, 402, 403, 404, 406, 407, 409, 411, 414, 501, 508, 603, 608, 618, 619, 621
Non-target tumors	3	212, 624, 626

10.1.1 Protocol Amendments

Date of Original Protocol: 10/10/99

Table 10.5 Protocol Amendments

Amendment Number	Issue Date	Description of Key Changes
1	01/21/00	Original protocol was not implemented, study redesigned in Amendment 1, changes to original protocol are not summarized here.
2	04/04/00	Sample amount for the measurements of temsirolimus and sirolimus concentrations reduced; third-party unblind

Amendment Number	Issue Date	Description of Key Changes
		was modified to include both the pharmacist and the pharmacokineticist; Temsirolimus dilution guidelines were revised to include calculations for dose modifications; updated instructions for handling VEGF samples; randomization section revised to reflect the outsourcing of the interactive voice response system to Interactive Clinical Technologies, Incorporated.
3	04/14/00	Site specific [redacted] research laboratory tests added.
4	07/24/00	Interim physical exam now monthly; added pre-medication with diphenhydramine; adjustment in dose modification for platelet toxicity; PBMC sample processing instructions changed; follow-up evaluation amended to include information regarding temsirolimus-related serious adverse events;
5	07/05/01	Modification of efficacy data analysis by providing for additional definitions of PD to reflect current practice of RECIST guidelines (25% increase in sum rather than individual lesions) and pre-study immunohistochemistry testing added if appropriate.
6	9/12/03	Site specific amendment to reflect change from ampules to vials; administrative changes;

10.1.2 Post Hoc Changes

Reviewer Comments: Amendment #5 issued 07/05/01 modified the efficacy data analysis to consider the change in the "sum of the products" as opposed to the initial plan to consider a "change in the size of one or more lesions or the appearance of new lesions". This change is deemed acceptable by this reviewer because it was made early in the trial and is consistent with current practice and more consistent with RECIST guidelines. The impact on the overall results is believed to be minimal because multiple techniques were proposed *including* the original technique of determining progression of disease. No other significant post hoc changes were noted that could possibly have impact upon the analysis.

10.1.3 Study Results

Disposition

The study was initiated on 4/11/00 and completed on 1/13/05. The 111 randomized, enrolled patients were randomly assigned in a 1:1:1 ratio to receive temsirolimus 25 mg (n=36), 75 mg (n=38), and 250 mg (n=37). A total of 110 patients received temsirolimus, and 44 (40% completed 8 treatment cycles. One patient who was randomized to receive 250 mg temsirolimus was not treated due to failure to meet inclusion/exclusion criteria. There were 105 patients evaluable for the assessment of efficacy.

One hundred six (106) patients discontinued treatment during the study. Disease progression was the most common reason for discontinuation in all 3 treatment groups. As of 8/12/02, 34 patients were in follow up. There were no discontinuations for protocol violations.

Demographics

Treatment groups did not vary significantly by ethnic origin, age, weight, or height. Variations between groups were seen in gender and ECOG performance status. The 25mg group was 67% male, the 75 mg group was 84% male, and the 250 mg group was 57% male. In the 25 mg group, 67% had an ECOG of 1; in the 75 mg group, 76% had an ECOG of 1; and in the 250 mg group 51% had an ECOG of 1.

Baseline Characteristics

Table 10.6: Demographic and Baseline Characteristics for the ITT Population By Treatment Group

	Treatment Group			
Characteristic	**25 mg (n=36)**	**75 mg (n=38)**	**250 mg (n=37)**	**Total (N=111)**
Ethnic origin, n (%)				
White	34 (94)	34 (89)	34 (92)	102 (92)
Black	0	2 (5)	1 (3)	3 (3)
Asian	0	0	0	0
Hispanic	2 (6)	2 (5)	2 (5)	6 (5)
Other	0	0	0	0
Sex, n (%)				
Female	12 (33)	6 (16)	16 (43)	34 (31)
Male	24 (67)	32 (84)	21 (57)	77 (69)
Age, years				
Mean	55.9	56.9	59.0	57.3
SD	8.3	11.9	10.7	10.4
Range	40-79	17-78	40-81	17-81
Weight, kg				
Mean	83.1	87.0	83.6	84.7
SD	19.5	25.5	19.1	21.6
Range	58-131	52-159	54-125	52-159
Height, cm				
Mean	173.6	174.7	173.2	173.8
SD	11.0	8.8	9.2	9.6
Range	157-206	154-190	155-188	154-206
ECOG performance status, n (%)				
0	12 (33)	9 (24)	18 (49)	39 (35)
1	24 (67)	29 (76)	19 (51)	72 (65)

Data from CDRs dmg_302b (23 Aug 2002), chx_306c (23 Aug 2002).

Efficacy

Primary Endpoint

The primary efficacy endpoint of this study was objective response rate. There were no complete responses reported. The median duration of treatment was 21 weeks, and 17 patients (15%) remained on treatment for at least 1 year. The definition of response was amended during the study with the end result being the "sum change definition" as called for in RECIST. The objective response rate was 7.2% using the sum change definition and the "clinical benefit rate" (objective response rate plus minor response plus stable disease for ≥ 8 weeks) was 71.2% using the sum change definition of tumor response. No statistically significant differences in objective tumor response was observed among the treatment groups.

Table 10.7 Tumor Response Rates by Protocol Definition in the ITT Population (N,%) (Applicant Table)

	Treatment Group			
Response	25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	Total (N=111)
Complete response	0	0	0	0
Partial response	2 (5.6)	1 (2.6)	3 (8.1)	6 (5.4)
Minor response	5 (13.9)	14 (36.8)	10 (27.0)	29 (26.1)
Stable disease[a]	13 (36.1)	11 (28.9)	9 (24.3)	33 (29.7)
Progressive disease	13 (36.1)	10 (26.3)	11 (29.7)	34 (30.6)
Unknown / no data	3 (8.3)	2 (5.3)	4 (10.8)	9 (8.1)

a: Duration of SD had to be at least 8 weeks ± 1 week.
Data from Stat_Report_200_final.doc (12 Sep 2002).

Table 10.8: Tumor Response Rates by Sum Change Definition in the ITT Population (N, %) (Applicant Table)

	Treatment Group			
Response	25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	Total (N=111)
Complete response	0	0	0	0
Partial response	2 (5.6)	3 (7.9)	3 (8.1)	8 (7.2)
Minor response	5 (13.9)	13 (34.2)	11 (29.7)	29 (26.1)
Stable disease[a]	20 (55.6)	11 (28.9)	11 (29.7)	42 (37.8)
Progressive disease	6 (16.7)	9 (23.7)	7 (18.9)	22 (19.8)
Unknown / no data	3 (8.3)	2 (5.3)	5 (13.5)	10 (9.0)

a: Duration of SD had to be at least 8 weeks ± 1 week.
Data from Stat_Report_200_final.doc (12 Sep 2002).

Secondary Endpoints

Duration of Response

The duration of response to therapy was a secondary endpoint measured in this study. The median duration of objective response was 8.45 months using the sum change definition and 5.46 months using the protocol definition. Because the number of objective responders was small in this study, median estimations presented in this section had wide ranges of confidence intervals. No discernable differences in duration of objective tumor response between treatment groups, using either the protocol definition or sum changes definition of response were seen.

Table 10.9: Time to and Duration of Objective Response (Applicant Table)

Treatment Group Patient Number	Protocol Definition		Sum Changes	
	Time to Response, days	Duration of Response, days	Time to Response, days	Duration of Response, days
25 mg				
134-612	344	111+	344	111+
933-303	58	99	58	288
75 mg				
13-203	-	-	337	393
13-207	-	-	60	257
933-304	59	155	59	155
250 mg				
13-206	67	166	67	166
13-209	288	261+	288	261+
933- 301	65	247	65	247

Data from Stat_Report_200_final.doc (12 Sep 2002). p.42 of appendix_nonsafety.pdf

Time to Tumor Progression

Time to tumor progression was also a secondary endpoint measured in this study. Median TTP was 3.6 months using the protocol definition and 5.8 months using the sum change definition. No differences in TTP were found between the treatment groups.

Table 10.10: Time to Tumor Progression Using the Protocol Definition (Applicant Table)

Value	Treatment Group 25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	Total (N=111)
Number (%) of patients whose tumors progressed	33 (92)	35 (92)	34 (92)	102 (92)
Median, months	3.5	3.7	3.6	3.6
95% confidence intervals	1.9–5.1	3.5–6.0	3.4–4.5	3.5–4.1
Progression-free rate at 8 weeks, %	67	74	77	73
Progression-free rate at 24 weeks, %	25	41	23	30

Data from Stat_Report_200_final.doc (12 Sep 2002).page 12 section 6.3.4.

Table 10.11: Time to Tumor Progression Using the Sum Change Definition (Applicant Table)

Value	Treatment Group 25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	Total (N=111)
Number (%) of patients whose tumors progressed	33 (92)	35 (92)	32 (87)	100 (90)
Median, months	6.3	6.7	5.2	5.8
95% confidence intervals	3.6–7.8	3.5–8.5	3.7–7.4	4.5–7.2
Progression-free rate at 8 weeks, %	86	76	83	82
Progression-free rate at 24 weeks, %	56	57	45	53

Data from Stat_Report_200_final.doc (12 Sep 2002) page 12 section 6.3.4

Progression-Free Survival
Progression-free survival was a secondary endpoint measured in this study. The differences between treatment groups were not significant.

Table 10.12: Progression-Free Survival by Protocol and Sum Change Definitions (Applicant Table)

temsirolimus Treatment Group	N with Progression or Who Died	Median months (95% CI) to progression or death[a]	Progression-free survival rate at 8 (24) weeks
(Protocol Definition)			
Overall (N=111)	104	3.60 (3.49–4.01)	70.91% (28.85%)
25 mg (N=36)	33	3.54 (1.91–5.13)	66.67% (25.00%)
75 mg (N=38)	36	3.63 (3.49–5.86)	71.05% (39.30%)
250 mg (N=37)	35	3.60 (3.42–4.24)	75.00% (22.22%)
(Sum Change)			
Overall	103	5.79 (3.85–7.17)	80.00% (51.59%)
25 mg	33	6.32 (3.59–7.76)	86.11% (55.56%)
75 mg	36	6.68 (3.49–8.49)	73.68% (55.14%)
250 mg	34	5.20 (3.72–7.40)	80.56% (43.65%)

a: Based on K-M estimation; 1 month = 30.4 days
Stat_report_200_final.doc

Change in ECOG performance status

At study week 4, the distributions of the change from baseline ECOG score were significantly different between the 25-mg and 250-mg treatment groups (p = 0.021). For the 25-mg treatment group, the performance status improved by 1 level in 6 patients (ECOG score decreased by 1 from baseline), and worsened by 1 level in 2 patients (ECOG score increased by 1 from baseline). For the 250-mg group, performance status did not improve in any patient and worsened by 1 level in 5 patients.

At study week 44, the ECOG score changes from baseline distributions were significantly different between the 25-mg and 250-mg treatment groups (p=0.028). In the 25-mg group, 1 patient had a decrease in ECOG score of 1 from baseline, and no patients had an increase in ECOG score of 1 from baseline; in the 250-mg group, no patient improved and 3 patients deteriorated in performance status.

No statistically significant differences in change from baseline ECOG scores were found among treatment groups at other ECOG score assessment time points.

Survival
Survival was a secondary endpoint measured in this study. The median total survival for all patients was 15.0 months. As of 03/31/04, 93 (84%) patients in the study had died. No statistically significant differences in survival were observed among the treatment groups.

Table 10.13: Long-Term Survival

Value	25 mg (n=36)	75 mg (n=38)	250 mg (n=37)	Total (N=111)
Median, months[a]	13.8	11.0	17.5	15.0
95% confidence interval	9.0–18.7	8.6–18.6	12.0–24.6	10.4–18.3
Number of deaths, n (%)	29 (81)	32 (84)	32 (86)	93 (84)

a: Based on Kaplan Meier estimation; 1 month = 30.4 days.
Data from survival report, death_033104_arm.ps, death_033104.ps

Proportion of progression-free patients
The proportion of patients progression-free at 8 weeks was a secondary endpoint measured in this study. No analysis of this outcome was provided in the study report.

Reviewer Comments: A subgroup analysis performed by the Applicant demonstrated that ECOG score at study entry was a significant predictor of response. Patients with a low ECOG (score 0) had a better chance of having clinical benefit than patients with higher ECOG (score 1). Therefore, the inequality of ECOG scores between groups would have potentially provided the 250 mg dose level with an advantage because it had more patients with an ECOG score of 0. Because the efficacy outcomes did not differ significantly between

Safety Analysis
Every patient who received temsirolimus in this study reported at least one adverse event (AE). There was no correlation between treatment group and percentage of patients reporting any AE. Likewise, there was no correlation between treatment group assignment and the number of clinical AEs of NCI toxicity grades 1 through 4 (p-value = 1), or AEs of NCI toxicity grades 3 and 4 (p=0.574).

Treatment Emergent Adverse Events reported for at least 30% of total patients were rash/maculopapular rash (76%) and pruritus (33%), mucositis (71%; includes stomatitis), asthenia (55%), nausea (47%), anorexia (42%), diarrhea (38%), cough increased (36%) and dyspnea (35%), infection (35%) and fever (30%), acne (35%), anemia (34%), vomiting (33%), and pain (33%).

Nausea was the only common TEAE to show a significant dose-toxicity relationship. Nausea was experienced by 13 patients (36%) in the 25-mg treatment group, 16 patients (42%) in the 75-mg group, and 23 patients (47%) in the 250-mg group (p=0.046 overall, 0.640 for the 25-mg vs 75-mg groups, 0.033 for the 25-mg vs 250-mg groups, and 0.068 for the 75-mg vs 250-mg groups).

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 most common drug-related TEAEs (experienced by at least 30% of the total

number of patients) were rash/maculopapular rash (76%), mucositis (70%), asthenia (50%), nausea (43%), anorexia (34%), acne (35%), pruritus (33%), and diarrhea (32%).

NCI grade 3 or 4 AEs were reported for 83 (76%) of patients in the study; 55% of patients experienced grade 3 or 4 laboratory abnormalities, which may or may not be associated with clinical symptoms. The TEAEs of NCI toxicity grade 3 or 4 reported for at least 5% of patients were hyperglycemia (20%), hypophosphatemia (16%), anemia (11%), dyspnea (10%), hyperlipemia (6%), pleural effusion (6%), and respiratory failure (5%). Of these, hyperglycemia, hypophosphatemia, anemia, and hyperlipemia represent clinical laboratory abnormalities. Only dyspnea and pleural effusion were symptomatic. Grade 3 or 4 drug-related TEAEs experienced by more than 5% of total patients were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hyperlipemia (6%). These are all TEAEs that represent clinical laboratory abnormalities.

For a more complete discussion of safety issues related to temsirolimus, please see Section 7 in the review body.

10.1.4 Conclusions

Temsirolimus demonstrated antitumor activity in patients with advanced renal cell carcinoma at all 3 dose levels tested. Increased exposure did not appear to confer a survival advantage. This study did not demonstrate significant differences in efficacy or toxicity between the three dose levels of temsirolimus tested. The overall response rate for all dose levels combined was 5.4% (based upon the protocol definition) or 7.2% (based on the sum change definition). A trend toward more dose reductions was seen in the higher dose arm. No statistically significant differences were seen between groups with regard to overall survival.

The Phase 3 dose selection for temsirolimus was 25mg IV weekly.

10.2 Line-by-Line Labeling Review

Labeling review will be described in a separate document.

Appears This Way
On Original

REFERENCES

1. American Cancer Society; www.cancer.org; retrieved 02/20/07.
2. Redman, BG, Kawachi, M, and Hurwitz, M. Urothelial and kidney cancers. In: Pazdur, R, Coia, LR, Hoskins, WJ, and Wagman, LD, ed. Cancer Management: A Multidisciplinary Approach. Lawrence, Kansas: CMP Healthcare Media; 2005:438-444.
3. Couillard DR, deVere White RW. Surgery of renal cell carcinoma. Urol Clin North Am. 1993;20:263-75.
4. Motzer, RJ, Mazumdar, M, Bacik, J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncology. 1999; 17: 2530-2540.
5. Kane, R. , 12/01/05, FDA Clinical Review, NDA 21923.
6. Goodman, V., 1/17/06, FDA Clinical Review, NDA 21968 N000.
7. Goodman, V., 01/25/07, FDA Clinical Review, NDA 21968 SE 007.
8. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. Ann Surg. 1998; 228: 307-319.
9. Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Fyfe G. High-dose aldesleukin in renal cell carcinoma: long-term survival update. Cancer J Sci Am. 1997;(suppl 1):S70-S72).
10. Messing EM, Manola J, Wilding G, et al: Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: An Eastern Cooperative Oncology Group/Intergroup Trial. J Clin Oncol 2003; 21:1214–1222.
11. Flanigan, RC, Salmon, SE, Blumenstein, BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001; 345:1655-1659 and Mickisch, GH, Garin, A, van Poppel, H., et al. European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. Lancet. 2001;358: 966-970.
12. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early study results of a randomized controlled trial. Lancet. 1999; 353: 14-17.
13. Pyrhonen S, Salminen E, Ruutu M, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol. 1999;17:2859-2867.
14. Atkins, MB, Hidalgo, M, Stadler, WM, Logan, TF, Dutcher, JP, Hudes, GR, Park, Y, Liou, S-H, Marshall, B, Boni, JP, Dukart, G, and Sherman, ML. Randomized Phase II Study of Multiple Dose Levels of CCI-779, a Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients With Advanced Refractory Renal Cell Carcinoma. JCO, 22(5), March 1 2004.
15. Draft Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics published in April 2005.

[i] 5.3.5.1, CSR-64508, Section 8.1; 2.7.3, Section 3.1.1

Appears This Way
On Original

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Kwitkowski
5/29/2007 09:42:16 AM
MEDICAL OFFICER

Tatiana Prowell
5/29/2007 10:56:28 AM
MEDICAL OFFICER

Amna Ibrahim
5/29/2007 11:40:39 AM
MEDICAL OFFICER