The Oncologist®

Regulatory Issues: FDA

FDA Approval Summary: Temsirolimus as Treatment for Advanced Renal Cell Carcinoma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Compare temsirolimus with IFN-α for the treatment of adults with treatment-naïve, advanced, poor-prognosis RCC and discuss the differences in OS time and PFS time for each.
2. Enumerate the laboratory parameters that should be monitored at baseline and while patients are receiving temsirolimus and implement appropriate laboratory monitoring procedures.

ABSTRACT

This report summarizes the U.S. Food and Drug Administration (FDA)'s approval of temsirolimus (Torisel®), on May 30, 2007, for the treatment of advanced renal cell carcinoma (RCC). Information provided includes regulatory history, study design, study results, and literature review.

A multicenter, three-arm, randomized, open-label study was conducted in previously untreated patients with poor-prognosis, advanced RCC. The study objectives were to compare overall survival (OS), progression-free survival (PFS), objective response rate, and safety in patients receiving interferon (IFN)-α versus those receiving temsirolimus alone or in combination with IFN-α.

In the second planned interim analysis of the intent-to-treat population (n = 626), there was a statistically significant longer OS time in the temsirolimus (25 mg) arm than in the IFN-α arm (median, 10.9 months versus 7.3 months; hazard ratio [HR], 0.73; p = .0078). The combination of temsirolimus (15 mg) and IFN-α did not lead to a significant difference in OS compared with

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IFN-α alone. There was also a statistically significant longer PFS time for the temsirolimus (25 mg) arm than for the IFN-α arm (median, 5.5 months versus 3.1 months; HR, 0.66, $p = .0001$).

Common adverse reactions reported in patients receiving temsirolimus were rash, asthenia, and mucositis. Common laboratory abnormalities were anemia, hyperglycemia, hyperlipidemia, and hypertriglyceridemia. Serious but rare cases of interstitial lung disease, bowel perforation, and acute renal failure were observed.

Temsirolimus has demonstrated superiority in terms of OS and PFS over IFN-α and provides an additional treatment option for patients with advanced RCC. *The Oncologist* 2010;15:428–435

INTRODUCTION

Temsirolimus (Torisel®; Wyeth Pharmaceuticals, Inc., Madison, NJ) (Fig. 1) is an inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. Temsirolimus prevents progression from the G_1 to S phase of the cell cycle through inhibition of mTOR and 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 variety of human tumor types in vitro and in vivo in nude mouse xenografts.

Temsirolimus is a prodrug of sirolimus, which is marketed as Rapamune® (Wyeth Pharmaceuticals, Inc., Madison, NJ) for the prophylaxis of organ rejection in patients aged ≥13 years following renal transplant [1]. Temsirolimus is administered as an i.v. infusion dosed at 25 mg weekly. A new drug application (NDA) for the indication of advanced renal cell carcinoma (RCC) was submitted to the U.S. Food and Drug Administration (FDA) in October 2006. Efficacy was demonstrated by a phase III randomized, open-label trial. A phase II dose-finding trial provided support for dose selection and safety.

RCC accounts for about 3% of cancer deaths, and an estimated 57,760 new diagnoses were made in 2009 [2]. For many years, surgery and immunotherapy have been the hallmarks of treatment for RCC. Surgical resection is appropriate for selected patients, including those with isolated metastases. However, RCC often recurs, even when the primary and metastatic sites are aggressively resected [3]. Metastatic RCC is typically highly resistant to standard chemotherapy. Even with multimodality therapy, the estimated average 5-year survival rate for patients diagnosed at stage 3 is 64%, and for stage 4 it is 23% [4].

Newer therapies, such as tyrosine kinase inhibitors and angiogenesis inhibitors, now make it possible to inhibit specific signals that promote tumor growth. From December 2005 through May 2007, three new drugs were approved by the FDA for RCC. Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) [5] and sunitinib (Sutent®; Pfizer, Inc., New York) [6, 7] received FDA marketing approval for advanced RCC based upon a longer progression-free survival (PFS) time than with placebo and interferon (IFN)-α, respectively.

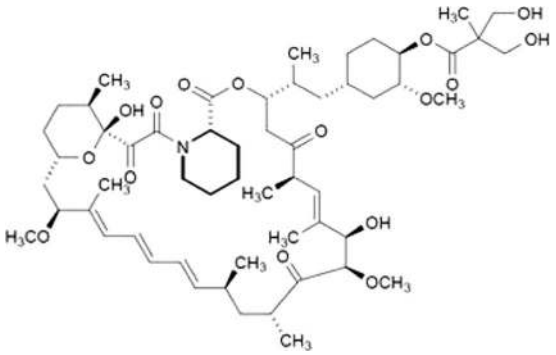

Figure 1. Chemical structure of temsirolimus. Molecular weight, 1030.3; molecular formula, $C_{56}H_{87}NO_{16}$.

Everolimus (Afinitor®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) was approved on March 30, 2009 for patients with advanced RCC after failure of sunitinib or sorafenib, based on a longer PFS time than with placebo. The median PFS time for patients treated with everolimus was 4.9 months (95% confidence interval [CI], 4.0–5.5), compared with 1.9 months (95% CI, 1.8–1.9) for those given placebo, with a hazard ratio (HR) of 0.33 ($p < .0001$) [8].

The final overall survival (OS) analysis for the randomized phase III sorafenib trial demonstrated confounding from crossover that occurred following announcement of a PFS benefit during a 2005 planned interim analysis of the trial (sorafenib, 17.8 months versus placebo, 15.2 months; HR, 0.88; $p = .146$) [9].

The analysis of OS, a secondary endpoint, in the phase III sunitinib trial showed a nonstatistically significant difference of 26.4 months versus 21.8 months (HR, 0.821; 95% CI, 0.673–1.001). In an exploratory analysis in which patients who crossed over to sunitinib after disease progression were censored, a longer OS time was observed. In that analysis, the median OS time for the sunitinib group was 26.4 months, compared with 20 months for the IFN-α group (HR, 0.808; 95% CI, 0.661–0.987) [10].

Table 1. Prognostic factors for RCC patients

● <1 yr from time of initial RCC diagnosis to randomization
● Karnofsky performance status score 60–70
● Hemoglobin < LLN
● Corrected calcium >10 mg/dl
● LDH >1.5× ULN
● >1 metastatic site of disease

Abbreviations: LDH, lactate dehydrogenase; LLN, lower limit of normal; RCC, renal cell carcinoma; ULN, upper limit of normal.

Table 2. Treatment arms for phase III trial

Arm (*n*)	Regimen
IFN-α (207)	3 MU s.c. 3× weekly for 1 wk → 9 MU s.c. 3× weekly for 2nd wk → 18 MU s.c. 3× weekly thereafter
Temsirolimus (209)	25 mg i.v. weekly
IFN-α + temsirolimus (210)	3 MU 3× weekly for 1 wk → 6 MU s.c. 3× weekly; 15 mg i.v. weekly

Abbreviation: IFN, interferon.

This exploratory analysis has not undergone FDA regulatory review.

The temsirolimus development plan was discussed in meetings between Wyeth and the FDA. The pivotal trial was submitted to the FDA for special protocol assessment in 2002, and agreement was reached on the acceptability of the treatment-naïve patient population, the use of IFN-α as a suitable comparator, and the selection of OS as the primary endpoint. Temsirolimus received fast-track designation for the treatment of first-line, poor-prognosis, advanced RCC in 2001 and orphan drug designation in 2004.

Patients and Methods

The results from the international, multicenter, phase III trial in the first-line treatment of advanced RCC provided the foundation of the efficacy and safety analysis for this NDA. That trial enrolled 626, treatment-naïve patients with advanced RCC and a poor prognosis (defined as having at least three of the six poor prognostic factors listed in Table 1). Eligible patients were randomized on a 1:1:1 basis to one of the three arms (IFN-α, temsirolimus, or the combination of IFN-α and temsirolimus) (Fig. 2). Dose modification was permitted in any arm, if either the temsirolimus or IFN-α doses were not tolerated. Randomization was stratified by nephrectomy status and region. The region strata were: (a) U.S.; (b) western Europe, Australia, and Canada; and (c) other (Asia-Pacific, eastern Europe, Africa, South America). Trial enrollment occurred between June 2003 and April 2005. At the time of the NDA submission, 30 patients were continuing to receive treatment and 124 patients were alive and in long-term follow-up after having discontinued treatment. The application contained the results of the second planned interim analysis.

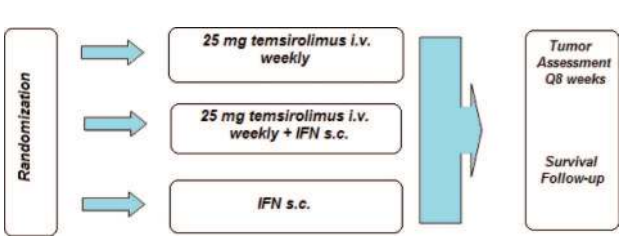

Figure 2. Phase III temsirolimus trial design.
Abbreviations: IFN, interferon; Q, every; s.c., subcutaneous.

The trial was designed with a primary endpoint of OS in the intent-to-treat (ITT) population. Secondary endpoints included the PFS time, overall response rate (ORR), and duration of objective response. The PFS duration was defined as the interval from the date of randomization until the earlier of the date of progression or death. Tumor assessments were performed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) at baseline and every 8 weeks until disease progression, even after discontinuation of study treatment. The modification of the RECIST allowed enrollment of patients with isolated bone metastases identified on magnetic resonance imaging. The PFS and ORR endpoints were based on a blinded central review to minimize the possibility of investigator bias. Disagreements between two blinded reviewers were adjudicated by a third independent radiology reviewer. Investigator assessments of tumor response were also performed for immediate clinical decision making, but investigator assessments were not used in the analysis of trial endpoints.

Eligibility criteria required that patients be adults with histologically confirmed, measurable disease according to the modified RECIST, a Karnofsky performance status score ≥60, adequate marrow, liver, and kidney function, a fasting serum cholesterol level ≤350 mg/dl, triglycerides ≤400 mg/dl, a life expectancy ≥8 weeks, and at least three of the six prognostic factors (Table 1) indicating a poor prognosis.

Exclusion criteria included prior anticancer therapy for RCC (except for nephrectomy and/or radiation), the use of investigational agents within 4 weeks of randomization, other malignancy within 5 years, lack of recovery from

Table 3. Demographics of intent-to-treat population

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, yrs			
Median	58	60	59
Mean	58.7	59.2	59.3
Range	32–81	23–86	32–82
Karnofsky performance status score, *n* (%)[a]			
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)
Region, *n* (%)			
U.S.	61 (29.1)	61 (29.4)	62 (29.5)
Western Europe, Australia, and Canada	44 (21)	43 (20.7)	42 (20)
Asia-Pacific, eastern Europe, Africa, South America	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)

[a]Numbers may not add up to 100% because one patient from each group had a missing value for baseline Karnofsky performance status score.
Abbreviation: IFN, interferon.

prior surgery or radiation therapy, immunocompromise resulting from HIV or hepatitis, active infection, serious illness, unstable angina or myocardial infarction within 6 months, cardiac arrhythmia, pulmonary hypertension, pneumonitis, pregnancy, breastfeeding, unwillingness to use an acceptable contraceptive device if of childbearing potential, and central nervous system metastasis unless asymptomatic, stable, and not steroid dependent following resection and/or radiation.

Protocol therapy was given weekly in repeating 28-day cycles and continued until disease progression or treatment withdrawal (Table 2) Patients receiving temsirolimus infusions were premedicated with an antihistamine 30 minutes before the infusion started. Patients receiving IFN-α were premedicated with acetaminophen 1–2 hours before injection. Study treatment was held until recovery for grade $\geq$3 toxicities that were drug related. Patients who discontinued treatment were followed for survival every 2 months.

Results

The baseline characteristics of the phase III study subjects are shown in Table 3. The patients were distributed evenly among the arms by gender, race, and age. The arms were generally well balanced for other baseline characteristics, although patients in the temsirolimus-containing arms had more favorable performance status scores. All the subjects had advanced, poor-prognosis RCC and had received no prior systemic therapy.

Efficacy

There was a statistically significant longer OS time in the temsirolimus (25 mg) arm than in the IFN-α monotherapy arm (median, 10.9 months versus 7.3 months; HR, 0.73; $p = .0078$) (Fig. 3 and Table 4). There was also a statistically significant longer PFS time for the temsirolimus (25 mg) arm than for the IFN-α monotherapy arm (median, 5.5 months versus 3.1 months; HR, 0.66; unadjusted $p = .001$). The combination of temsirolimus (15

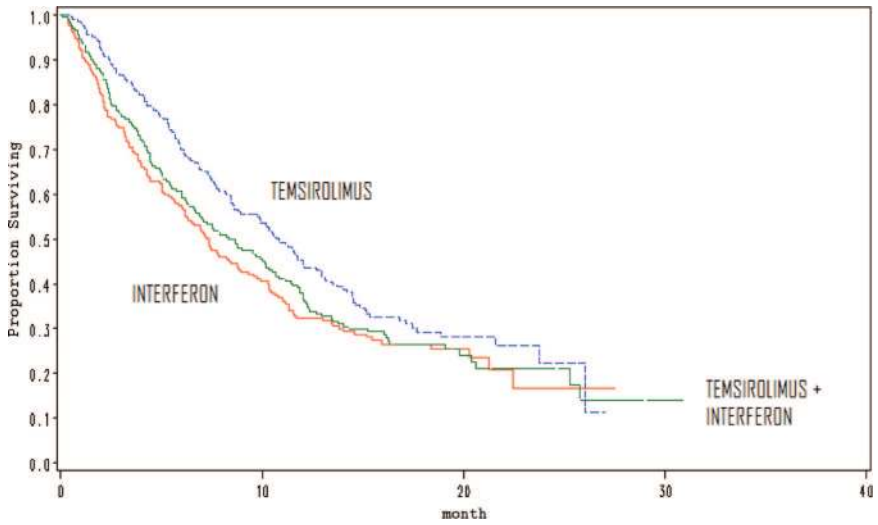

Figure 3. Overall survival in intent-to treat population.

mg) and IFN-α resulted in greater toxicity and no statistically significant difference in OS when compared with IFN-α alone.

The median follow-up durations for the surviving subjects were similar among treatment arms at 16.3 months (IFN-α), 17 months (temsirolimus), and 17 months (temsirolimus plus IFN-α). Because OS did not differ significantly between the combination arm and the IFN monotherapy arm, the secondary efficacy endpoint results for the comparison between these two arms are not discussed further. The results of the subgroup analyses of OS stratified by nephrectomy status and region were consistent with the results in the overall ITT population. The analyses of OS and PFS by age, sex, and race were also consistent with the results for the overall ITT population.

Other secondary efficacy endpoints included the ORR and duration of objective response. Based upon an independent assessment, the ORR was 8.6% in the temsirolimus arm versus 4.8% in the IFN-α arm ($p = .12$). All responses were partial responses. The median durations of response were 11.1 months in the temsirolimus arm and 7.4 months in the IFN-α arm. In summary, treatment with temsirolimus resulted in a longer median OS time and median PFS time than with IFN-α. The difference in ORR was not statistically significant.

Table 4. Survival duration for intent-to-treat population

Variable	Temsirolimus ($n = 209$)	IFN-α ($n = 207$)
Subjects who died	143	149
Censored observations	58 (28%)	66 (31.6%)
Duration of survival, mos		
Median	10.9	7.3
95% CI	(8.6–12.7)	(6.1–8.8)
Stratified analysis		
Hazard ratio[a]	0.73	
95% CI	(0.58–0.92)	
p-value (log rank)	.0078	

[a]Relative to IFN-α. The strata are region and nephrectomy status.
Abbreviations: CI, confidence interval; IFN, interferon.

Safety

In the phase III study, safety monitoring included clinical assessments, laboratory parameter assessments, and electrocardiograms. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria, version 3.0. Single-agent temsirolimus was associated with a lower overall incidence of grade 3 and 4 adverse reactions and serious adverse events than IFN-α or the combination. The incidence of adverse reactions leading to treatment discontinuation and dose reduction was also lowest in the temsirolimus monotherapy arm, although this arm had a higher incidence of adverse reactions resulting in dose delays.

Table 5 displays the most common and serious adverse reactions and laboratory abnormalities seen in patients treated with temsirolimus. The most common nonlaboratory-related adverse reactions in the temsirolimus arm were asthenia (51%), rash (47%), and mucositis (41%). The most common grade 3 or 4 nonlaboratory-related adverse reactions reported in patients receiving temsirolimus were asthenia (11%), dyspnea (9%), and rash (5%).

The most common clinically important laboratory abnormalities in the temsirolimus arm were anemia (94%), hyperglycemia (89%), hyperlipidemia (87%), and hypertri-

Table 5. Adverse reactions and laboratory abnormalities reported in ≥10% of patients who received temsirolimus in the randomized trial (safety population)

	Temsirolimus, 25 mg ($n = 208$)		IFN-α ($n = 200$)	
Adverse reaction	**All grades[a] *n* (%)**	**Grades 3 and 4[a] *n* (%)**	**All grades[a] *n* (%)**	**Grades 3 and 4[a] *n* (%)**
Any adverse reaction	208 (100)	139 (67)	199 (100)	155 (78)
General disorder				
Asthenia	106 (51)	23 (11)	127 (64)	52 (26)
Edema[b]	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)	50 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest pain	34 (16)	2 (1)	18 (9)	2 (1)
Gastrointestinal disorder				
Mucositis[c]	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)
Infection				
Infection[d]	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection[e]	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 or connective tissue disorder				
Back pain	41 (20)	6 (3)	28 (14)	7 (4)
Arthralgia	37 (18)	2 (1)	29 (15)	2 (1)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea	58 (28)	18 (9)	48 (24)	11 (6)
Cough	53 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
Skin or s.c. tissue disorder				
Rash[f]	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 disorder				
Dysgeusia[g]	41 (20)	0 (0)	17 (9)	0 (0)
Insomnia	24 (12)	1 (1)	30 (15)	0 (0)
Any laboratory abnormality	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Anemia	195 (94)	41 (20)	180 (90)	43 (22)

(continued)

Table 5. (Continued)

Adverse reaction	Temsirolimus, 25 mg ($n = 208$)		IFN-α ($n = 200$)	
	All grades[a] n (%)	Grades 3 and 4[a] n (%)	All grades[a] n (%)	Grades 3 and 4[a] n (%)
Lymphocytopenia	110 (53)	33 (16)	106 (53)	48 (24)
Neutropenia	39 (19)	10 (5)	58 (29)	19 (10)
Thrombocytopenia	84 (40)	3 (1)	51 (26)	0 (0)
Chemistry				
↑ Alkaline phosphatase	141 (68)	7 (3)	111 (56)	13 (7)
↑ Aspartate aminotransferase	79 (38)	5 (2)	103 (52)	14 (7)
↑ Creatinine	119 (57)	7 (3)	97 (49)	2 (1)
Hyperglycemia	186 (89)	33 (16)	128 (64)	6 (3)
Hypophosphatemia	102 (49)	38 (18)	61 (31)	17 (9)
↑ Total bilirubin	16 (8)	2 (1)	25 (13)	4 (2)
Hypercholesterolemia	181 (87)	5 (2)	95 (48)	2 (1)
Hypertriglyceridemia	173 (83)	92 (44)	144 (72)	69 (35)

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

glyceridemia (83%). The most frequently reported grade 3 or 4 laboratory abnormalities in the temsirolimus arm were hypertriglyceridemia (44%), anemia (20%), hypophosphatemia (18%), and hyperglycemia (16%). Many patients who experienced hyperglycemia and hypertriglyceridemia required treatment. The overall incidence of grade 3 and 4 laboratory abnormalities on treatment was higher in the temsirolimus arm (78%) than in the IFN-α monotherapy arm (72%).

Rare serious adverse reactions, in some cases resulting in death, associated with i.v. temsirolimus use included interstitial lung disease (ILD), bowel perforation, and acute renal failure. Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received temsirolimus. Some of these cases were not responsive to dialysis.

In the phase III trial, pneumonitis was reported in five patients in the temsirolimus arm, compared with one patient each in the IFN-α and the combination arms. Several other pulmonary adverse events were also reported more commonly in patients who received temsirolimus. This safety signal suggests that a heightened awareness of symptoms consistent with ILD is needed as more patients are exposed to temsirolimus.

Mucositis occurred more commonly in patients receiving temsirolimus (41%) than in those receiving IFN-α (10%). Two cases of bowel perforation were diagnosed in the phase III trial, one in the temsirolimus arm and one in the combination arm. Seven cases of bowel perforation, including four fatalities, were identified across the entire temsirolimus safety database. Autopsy was performed on one patient, which demonstrated grade 4 mucositis with multiple associated perforations in the rectal mucosa. Because bowel perforation is frequently fatal if not recognized promptly and appropriately treated, prescribing physicians should monitor closely for symptoms that may represent bowel perforation in patients receiving temsirolimus, particularly in patients who experience severe mucositis.

Clinically important drug–drug interactions exist between potent cytochrome P450 (CYP)3A4 inducers and sirolimus, which is the primary metabolite of temsirolimus. A weekly i.v. dose of 50 mg temsirolimus should be considered in patients who must receive a concurrent potent CYP3A4 inducer. Interactions similarly exist between potent CYP3A4 inhibitors and sirolimus. For patients receiv-

ing a concurrent potent CYP3A4 inhibitor, a weekly i.v. dose of 12.5 mg temsirolimus should be considered.

Discussion

RCC is often advanced at the time of diagnosis and refractory to standard chemotherapy. IFN-α was an appropriately active comparator for temsirolimus in this population because, although it does not have FDA approval for this indication, it has historically been a commonly used agent for advanced RCC and has demonstrated a survival advantage in previous comparative trials [11, 12].

In a phase III, multicenter, randomized trial, temsirolimus was compared with IFN-α alone (or in combination with temsirolimus) in the treatment of adults with treatment-naïve, advanced, poor-prognosis RCC. An interim analysis of OS demonstrated a statistically significant and clinically meaningful longer OS time in the temsirolimus arm than in the IFN-α arm. The difference in OS was the primary basis of the FDA approval for temsirolimus.

Notable toxicities associated with the use of temsirolimus include asthenia, rash, and mucositis. Patients receiving temsirolimus also had a high incidence of laboratory abnormalities, particularly anemia, hyperglycemia, and hyperlipidemia, that often required treatment. ILD, bowel perforation, infusion reactions, and acute renal failure are rare, sometimes fatal, complications of temsirolimus use.

Because of the frequency of laboratory-related adverse reactions requiring treatment, the clinician should monitor the following laboratory parameters at baseline and while patients are receiving temsirolimus: renal function, hepatic function, lipid profile, glucose, phosphate, and CBC. It is recommended that patients be pretreated with an antihistamine before every dose of temsirolimus. Since its approval, one case of a fatal infusion reaction during the first few minutes of the first treatment was reported. Patients should be informed of the risk for infusion reactions and observed closely throughout infusion.

Conclusions

Temsirolimus is indicated as a single agent for the treatment of adults with advanced RCC. Temsirolimus has demonstrated superiority in terms of OS and PFS over IFN-α and provides an additional treatment option for patients with advanced RCC. The combination of temsirolimus with IFN-α was associated with greater toxicity and no difference in efficacy.

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