

Temsirolimus for advanced renal cell carcinoma

The gamut of therapeutic options for patients with advanced kidney cancer widens with the recent approval of a novel mTOR kinase inhibitor

What's new, what's important

Temsirolimus (Torisel) received approval from the US Food and Drug Administration as first-line treatment of metastatic renal cell carcinoma. It is a mammalian target of rapamycin (mTOR) kinase inhibitor, an enzyme that has an important role in regulating the synthesis of proteins that control cell division.

The recommended initial dose of temsirolimus is 25 mg, infused over a period of 30–60 minutes once weekly. Patients should be premedicated with intravenous diphenhydramine, 25–50 mg, or a similar antihistamine approximately 30 minutes before the start of each dose.

Concomitant use of cytochrome P450 3A4 (CYP3A4) inducers and inhibitors should be avoided, if possible. CYP3A4 inhibitors such as ketoconazole or clarithromycin will increase the serum level of temsirolimus, necessitating a reduction in its dose to 12.5 mg/wk. When temsirolimus is used with CYP3A4 inducers such as dexamethasone, carbamazepine, or phenytoin, the dose may be increased up to 50 mg/wk.

The most common adverse reactions of temsirolimus, seen in at least 30% of patients who were treated with the drug in clinical trials, were rash, fatigue, mouth sores, nausea, edema, and loss of appetite.

Hopefully, the specific role of this agent in the treatment of renal cell carcinoma in relationship to two other targeted therapies, sorafenib (Nexavar) and sunitib (Sutent), will soon be clarified.

— Jame Abraham, MD
Section Editor

Temsirolimus (Torisel), a mammalian target of rapamycin (mTOR) kinase inhibitor, was recently approved for use in treating advanced renal cell carcinoma (RCC). This agent forms a complex with the intracellular protein FKBP-12; the complex inhibits mTOR signaling, down-regulating the production of proteins involved in cell-cycle regulation and angiogenesis.^{1,2} Increased angiogenesis is a prominent feature of RCC.³

Approval of temsirolimus was based, in part, on a randomized phase III trial comparing temsirolimus alone with interferon alfa-2a (IFN- α ; Roferon-A) alone and a combination of temsirolimus and IFN- α in

previously untreated patients with advanced RCC.⁴ A prior phase II trial showed that the agent produced objective and minor responses and was generally well tolerated in patients with advanced refractory RCC.⁵

Phase III study results

In the phase III trial, 626 treatment-naïve, poor-prognosis patients with metastatic RCC received temsirolimus (25 mg IV weekly), IFN- α (3 million U SC to start, followed by an increase to 18 million U SC 3 times weekly), or a combination of temsirolimus (15 mg IV weekly) plus IFN- α (6 million U SC 3 times weekly). The patients had a median age of 59 years and were predomi-

nantly (69%) male. In all, 94% of the patients had at least three protocol-defined poor prognostic features, including a serum lactate dehydrogenase (LDH) level > 1.5 times the upper limit of normal, a serum hemoglobin level below the lower limit of normal, a corrected serum calcium level > 10 mg/dL, < 1 year from the time of initial diagnosis to study randomization, a Karnofsky performance score \leq 70, and multiple organ metastases.

On a second interim analysis (after 446 deaths), an overall survival (OS) difference was found to exceed the prespecified *P* value of < 0.0135 for stopping the study. Temsirolimus alone was associated with a 27% reduction in risk for death (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.58–0.92; *P* = 0.008) and significantly greater progression-free survival (*P* < 0.001) compared with IFN- α alone. Median OS was 10.9 months with temsirolimus alone, 7.3 months with IFN- α alone, and 8.4 months with the combination (Table 1); however, median OS in the combination group did not significantly differ from that in the IFN- α group.

The benefit of temsirolimus versus IFN- α alone was consistent across patient subgroups (Figure 1), except for an interaction of treatment with age and with LDH level; the benefit of temsirolimus was greater in younger than in older patients and in those with higher versus lower LDH levels. There were no differences among treatment groups with regard to ob-

Summary by Matt Stenger, MS; reviewed by Kevin B. Knopf, MD, MPH, California Pacific Medical Center, San Francisco, CA.

jective response rates (Table 1); significantly more patients in the temsirolimus group (32.1%; $P < 0.001$) and in the combination group (28.1%; $P = 0.002$) had clinical benefit (objective response or stable disease for ≥ 24 weeks) compared with the group treated with IFN- α alone (15.5%).

Adverse events

Adverse events are shown in Table 2. Overall, grade 3 or 4 adverse events were significantly more common with IFN- α (78%; $P = 0.02$) and combination treatment (87%; $P = 0.02$) than with temsirolimus alone (67%). Among grade 3 or 4 adverse events, asthenia was significantly more common with IFN- α or combination treatment than with temsirolimus alone. Overall, patients receiving temsirolimus alone or in combination had higher frequencies of mild to moderate rash, peripheral edema, and stomatitis compared with those who received IFN- α alone. Anemia, neutropenia, and thrombocytopenia were significantly more common in the combination group than in the groups receiving either agent alone. Presumably because mTOR is involved in glucose and lipid metabolism, hyperglycemia and hyperlipidemia were more common in the temsirolimus and combination groups than in the IFN- α group. Dose delivery was approximately 56% of maximum planned dose with IFN- α alone, 92% with temsirolimus alone, and 72% and 73% for IFN- α and temsirolimus, respectively, in the combination group. At least one dose reduction was required for 39% of patients with IFN- α alone, 23% with temsirolimus alone, and 48% and 30% with IFN- α and temsirolimus, respectively, in the combination group. At least one dose delay was required for 68% of patients with IFN- α alone, 66% with temsirolimus alone, and 86% and 82% with IFN- α and temsirolimus, respectively, in the combination group.

Torisel labeling includes warnings about hypersensitivity reactions, hyperglycemia, immunosuppression-

TABLE 1

Efficacy outcomes in a phase III trial of temsirolimus in patients with advanced renal cell carcinoma

	IFN- α (n = 207)	Temsirolimus (n = 209)	IFN- α + temsirolimus (n = 210)
Median overall survival, mo	7.3	10.9	8.4
Median progression-free survival, mo:			
Investigator assessment	1.9	3.8	3.7
Independent assessment*	3.1	5.5	4.7
Median time to treatment failure (investigator judged), mo	1.9	3.8	2.5
Objective response rate	4.8%	8.6%	8.1%
Clinical benefit rate (objective response or stable disease for ≥ 24 wk)	15.5	32.1	28.1

IFN- α = interferon alfa

* Blinded assessment of imaging studies in 153 patients in the interferon- α group, 192 in the temsirolimus group, and 168 in the combination group.

Adapted, with permission from, Hudes et al⁴

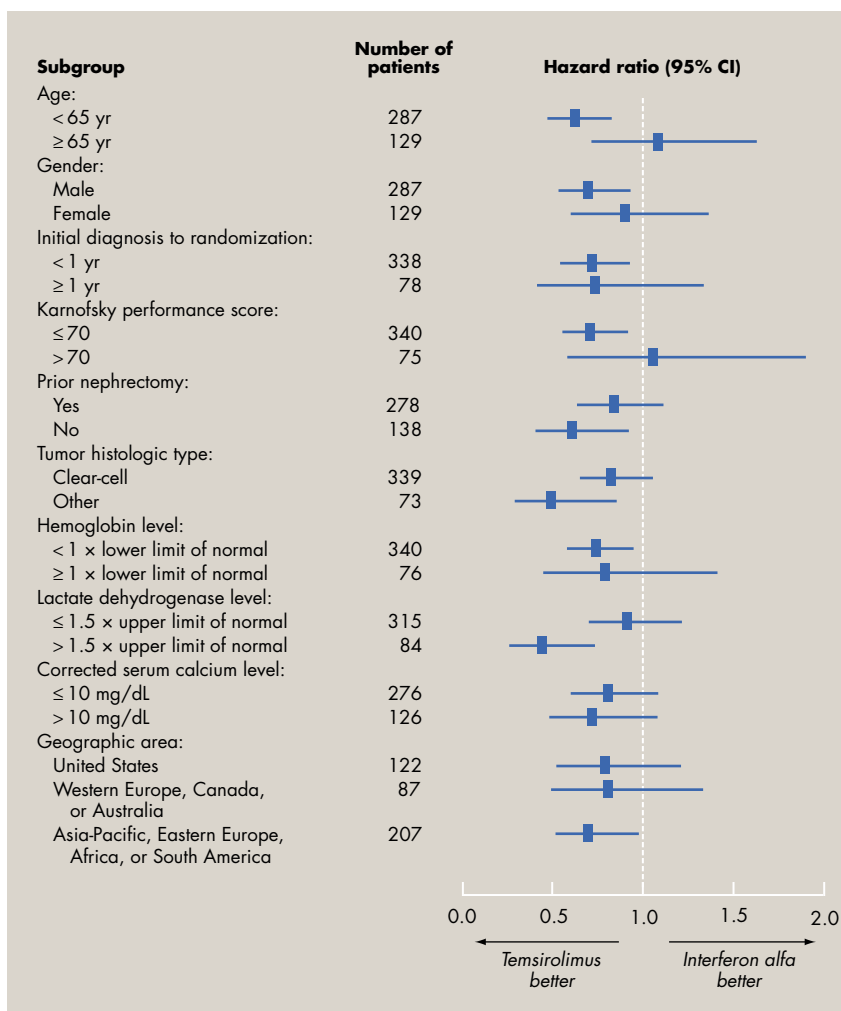


FIGURE 1 Hazard ratios for overall survival in patients with advanced renal cell carcinoma receiving temsirolimus alone or interferon alfa alone in a phase III trial. CI = confidence interval. Adapted, with permission, from Hudes et al.⁴

TABLE 2

Adverse events occurring in $\geq 25\%$ of patients in any of the treatment arms of a phase III trial of temsirolimus in advanced renal cell carcinoma

Adverse event	Percentage of patients					
	IFN- α (n = 200)		Temsirolimus (n = 208)		IFN- α + temsirolimus (n = 208)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Asthenia	64	26	51	11	62	28
Rash	6	0	47	4	21	1
Anemia	42	22	45	20	61	38
Nausea	41	4	37	2	40	3
Anorexia	44	4	32	3	38	8
Pain	16	2	28	5	20	6
Dyspnea	24	6	28	9	26	10
Hyperlipidemia	14	1	27	3	38	8
Infection	14	4	27	5	34	11
Diarrhea	20	2	27	1	27	5
Peripheral edema	8	0	27	2	16	0
Hyperglycemia	11	2	26	11	17	6
Cough	14	0	26	1	23	2
Fever	50	4	24	1	60	3
Vomiting	28	2	19	2	30	2
Weight loss	25	2	19	1	32	6
Increased creatinine level	10	1	14	3	20	3
Thrombocytopenia	8	0	14	1	38	9
Chills	30	2	8	1	34	1
Neutropenia	12	7	7	3	27	15
Leukopenia	17	5	6	1	31	9

IFN- α = interferon alfa

Adapted, with permission, from Hudes et al⁴

related infections, interstitial lung disease, hyperlipidemia, bowel perforation, renal failure, wound-healing complications, intracerebral hemorrhage, and concomitant use with sunitinib (Sutent), the multitargeted receptor tyrosine kinase inhibitor also approved for the treatment of advanced RCC. Temsirolimus is metabolized by CYP3A4 isoenzymes, and the dosage must be adjusted with concomitant administration of inhibitors or inducers of this enzyme.

References

1. Hay N, Sonenberg N. Upstream and downstream of mTOR. *Genes Dev* 2004;18:1926–1945.
2. Del Bufalo D, Ciuffreda L, Triscioglio D, et al. Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus. *Cancer Res* 2006;66:5549–5554.
3. Pantuck AJ, Zeng G, Beldegrun AS, Figlin RA. Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. *Clin Cancer Res* 2003;9:4641–4652.
4. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–2281.
5. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;22:909–918.

From the Community Oncologist's Perspective

Another step forward in RCC

Kevin B. Knopf, MD, MPH | California Pacific Medical Center, San Francisco, CA

Before 2006, interferon alfa-2a (Roferon-A) and interleukin-2 (aldesleukin; Proleukin) were the mainstays of therapy used to treat kidney cancer in community practice, with some patients occasionally responding to cytotoxic chemotherapy. The clinical benefit was certainly suboptimal, and one was left to wonder how much of an impact we were making against renal cell cancer

(RCC). Durable responses were primarily seen with high-dose aldesleukin, which not all oncologists were comfortable administering; the drug was highly toxic and appropriate only for a subset of patients.

Now we have a third new drug that has been approved by the US Food and Drug Administration for the treatment of RCC, following on the heels of sorafenib (Nexavar) and sunitinib (Sutent). Temozolomide (Temodar), an inhibitor of the mammalian target of rapamycin kinase, seems relatively straightforward to administer with a “traditional cytotoxic” profile, apart from a novel need to monitor and possibly treat patients for hyperlipidemia.

What makes the use of temsirolimus a little challenging is the availability of three new agents for the treatment of RCC. Questions remain

regarding sequencing and patient selection for each agent. Some features of the temsirolimus clinical trials may elucidate these questions.

In a dose-ranging phase II study of temsirolimus, Atkin and colleagues¹ observed a doubling of median survival in patients with metastatic RCC and a poor prognosis. These patients had a Karnofsky performance status of 60%–70%, developed metastatic disease within a year of initial diagnosis, and had a serum lactate dehydrogenase level > 1.5 times the upper limit of normal, a below-normal hemoglobin level, a corrected serum calcium concentration > 10 mg/L, and/or two or more organ sites of involvement. This was the group chosen for the randomized phase III study,² which confirmed the results of the earlier study.

Based on a presentation by Dutcher et al³ at this year's American Society of Clinical Oncology (ASCO) annual meeting, it also seems that temsirolimus is the drug of choice in the 15%

of patients with RCC of non-clear cell histology. The analysis by Dutcher and colleagues also showed that RCC patients with intermediate-risk features benefit from temsirolimus. However, it is unclear whether "good risk" patients would derive similar benefit. Thus, choosing among the agents available for this subset of patients continues to be a challenge.

Other studies presented at the ASCO 2007 meeting show that patients can respond to sunitinib after sorafenib and vice versa. Changes in dosage and schedule yielded interesting results, and combinations of these agents in RCC are under investigation. At least four other drugs also showed promising activity in phase II studies.

Choosing a first-line agent for metastatic RCC will pose a challenge, but it is a welcome challenge to have. The likely approval of bevacizumab (Avastin) and interferon alfa-2a based on the multinational AVOREN trial,⁴

will add another welcome therapeutic option for clinical oncologists. The treatment of RCC has become more complex, due to the availability now of four novel, and, fortunately for patients, more effective agents.

References

1. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;22:909–918.
2. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon-alfa or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–2891.
3. Dutcher JP, Szczylik C, Tannir N, et al. Correlation of survival with tumor histology, age, and prognostic risk group with advanced renal cell carcinoma receiving temsirolimus or interferon-alfa. *J Clin Oncol* 2007;25(18S):5033.
4. Escudier B, Koralewski P, Pluzanska A, et al. A randomized, controlled, double-blind phase II study (AVOREN) of bevacizumab/interferon- α 2a vs placebo/interferon- α 2a as first-line therapy in metastatic renal cell carcinoma. *J Clin Oncol* 2007;25(18S):3.

E-mail Dr. Knopf at leroy@alum.mit.edu.