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Temsirolimus
In Advanced Renal Cell Carcinoma

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Contents

Abstract

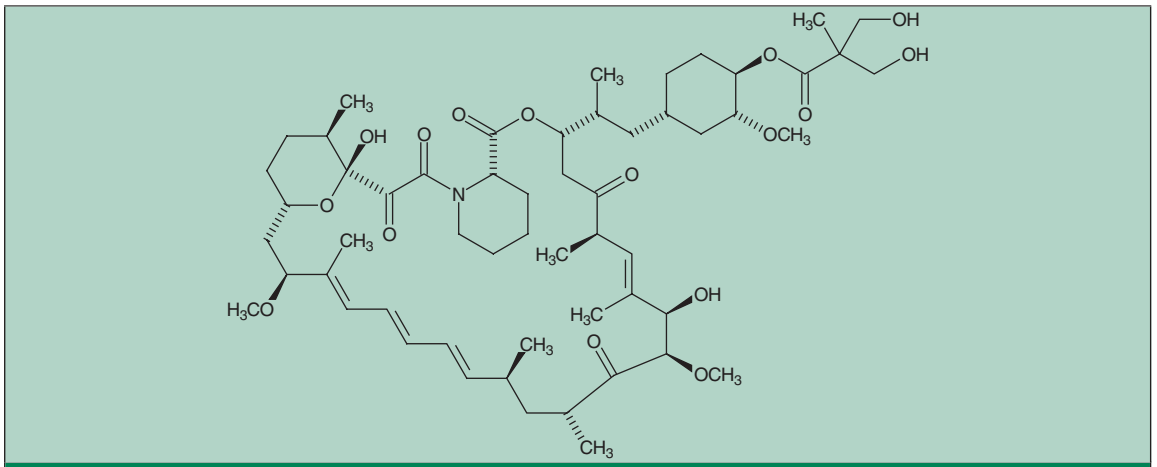
▲ Temsirolimus, an ester of sirolimus (rapamycin), selectively inhibits the kinase mammalian target of rapamycin and consequently blocks the translation of cell cycle regulatory proteins and prevents the over expression of angiogenic growth factors.

▲ Patients with advanced renal cell carcinoma and a poor prognosis who received a once-weekly intravenous infusion of temsirolimus 25 mg experienced significant survival benefits compared with patients receiving standard interferon-α (IFNα) therapy (3–18 MU subcutaneously three times weekly) in a large phase III clinical study. Median overall survival was 10.9 versus 7.3 months, progression-free survival was 5.5 versus 3.1 months.

▲ Objective response rates were 8.6% in temsirolimus recipients versus 4.8% in IFNα recipients.

▲ Temsirolimus monotherapy recipients experienced significantly fewer grade 3 or 4 adverse events and had numerically fewer withdrawals for adverse events than patients receiving IFNα.

Features and properties of temsirolimus (CCI-779; Torisel™)	
Indication	
Advanced renal cell carcinoma	
Mechanism of action	
Mammalian target of rapamycin inhibitor	
Dosage and administration	
Dose	25 mg
Route of administration	Intravenous (IV) infusion over a 30–60 min period
Frequency of administration	Once weekly
Pharmacokinetic profile of a single IV infusion of temsirolimus 25 mg in patients with advanced renal cell carcinoma	
Peak concentration in whole blood (C_{max})	595 μg/L
Time to C_{max}	≈0.5 h
Area under the concentration-time curve in whole blood	1580 μg • h/L
Volume of distribution at steady state	232 L
Adverse events	
Most frequently reported	Asthenia, rash, anaemia, nausea, anorexia



Renal cell carcinoma accounts for 2–3% of all cancers diagnosed worldwide.[1,2] When diagnosed before the disease has metastasized (stage I–III), renal cell carcinoma may be treated surgically. However, at least 25% of patients present with stage IV or advanced (metastatic) disease, which has a median survival time of 10–12 months.[3]

Most renal cell cancers (85%) are classified histologically as clear cell type. These tumours are typically (>80%) characterized by a loss of expression of a functional von Hippel-Lindau (VHL) gene.[2,4] This gene regulates protein stability of hypoxia-inducible transcription factors (HIF) 1α and 2α. Loss of VHL function prevents the degradation of these factors and leads to their accumulation, with the subsequent increased expression of HIF-regulated proteins such as vascular endothelial growth factor (VEGF) and other angiogenic and growth-stimulating molecules.

Prior to the introduction of targeted cancer therapies, there were limited options for systemic therapy (which may or may not follow surgery) in patients with renal cell carcinoma.[5] Cytokine-based immunotherapy with interleukin-2 (IL-2) and interferon-α (IFNα) are associated with modest objective response rates of 10–15% and substantial toxicity.[4,6] Moreover, a survival advantage for treatment with these agents has been difficult to establish.[4,5] A better understanding of the pathogenesis of renal cell carcinoma, particularly the role of tumour angiogenesis, has led to the development new therapeutic agents, with VEGF or the mammalian target of rapamycin (mTOR) being targeted.[5]

Temsirolimus (Torisel™)[1] is a selective inhibitor of mTOR, a serine/threonine kinase involved in controlling many cellular functions such as cell proliferation, cell survival, protein synthesis and transcription of HIF-α.[2,4]

This article reviews the pharmacological profile, therapeutic efficacy and tolerability of temsirolimus 25 mg administered as a 30- to 60-minute intravenous infusion once weekly in patients with advanced renal cell carcinoma.

1. Pharmacodynamic Profile

- Temsirolimus, an ester of sirolimus (rapamycin), is a small molecule inhibitor that selectively binds to the immunophilin FK506-binding protein 12 kDa isoform (FKBP12) to form a complex with mTOR.[7-9]
- When mTOR is bound in this complex, it is unable to phosphorylate protein translation factors,

1 The use of trade names is for identification purposes only and does not imply endorsement.

namely the eukaryotic initiation factor 4E binding protein-1 and the S6 kinase (also known as p70S6 kinase), which are downstream of mTOR in the phosphatidylinositol 3-kinase/Akt/mTOR pathway.[8,10] Thus the translation of several key proteins regulating the cell cycle is inhibited and the cell cycle is blocked at the G1 phase.[4]

- The disruption of mTOR by temsirolimus can also suppress the production of proteins that regulate angiogenesis (unregulated angiogenesis is prominent in renal cell carcinoma) and other growth stimulating molecules.[11,12] *In vitro* studies demonstrate that temsirolimus can regulate the translation of HIF-1α and HIF-2α and the production of the angiogenic factor VEGF.[2,4,13-15] The anti-angiogenic effect of temsirolimus has been demonstrated in breast cancer cell lines and *in vivo* models of cancer (rhabdomyosarcoma).[13,16]
- Temsirolimus demonstrated anti-proliferative activity in a range of *in vitro* human tumour cell lines, including prostate and breast cancer.[13,17]
- Temsirolimus demonstrated activity in a range of *in vivo* human tumour mouse xenograft models (including renal cancer).[16-19] In a nude mouse human renal cell carcinoma (A498) xenograft model, temsirolimus alone showed cytostatic effects, and induced tumour regression when combined with IFN-α.[20]

2. Pharmacokinetic Profile

The pharmacokinetic data for temsirolimus administered as a once-weekly 30-minute intravenous infusion in patients with advanced renal cancer reviewed in this section has primarily been derived from a phase II study[21] and the manufacturer's prescribing information.[18]

- In patients (n ≤4) with advanced renal cell carcinoma who received a single dose of temsirolimus 25 mg as a 30-minute intravenous infusion, mean peak concentration (C_{max}) in whole blood was 595 μg/L, mean time to C_{max} was 0.51 hours, the mean area under the concentration-time curve (AUC) in whole blood was 1580 μg • h/L.[21] The C_{max} and AUC of temsirolimus increased less than proportionately with increasing dose over the dose range 1–25 mg.[18]
- A population pharmacokinetic-based data analysis indicated that there was no relationship between drug exposure and patient age, gender or race.[22]
- Following administration of a single intravenous dose of temsirolimus 25 mg, the AUC of sirolimus (3810 μg • h/L) was approximately twice that of temsirolimus, principally due to the longer terminal elimination half-life of sirolimus versus temsirolimus (48.8 vs 12.8 hours).[21] Sirolimus appeared soon after (i.e. within 15 minutes[23]) temsirolimus administration and the mean sirolimus C_{max} was typically 10–20% of the parent drug C_{max},[21] increasing proportionately with an increasing dose.[18]
- There was extensive tissue distribution of temsirolimus; for patients receiving 25 mg intravenous once weekly, the volume of distribution at steady state in whole blood of patients with renal cancer was 232 L and the total body clearance was 16.1 L/h, both of which were increased in patients receiving higher doses.[21] Both temsirolimus and sirolimus are extensively partitioned into formed blood elements.[18]
- Temsirolimus is metabolized primarily by cytochrome P450 (CYP) 3A4,[18] as is sirolimus, its principal (and equipotent[24]) metabolite.[18]
- Excretion of a single dose of intravenous [^{14}C]temsirolimus was primarily via the faeces (78%), with renal excretion accounting for 4.6% of the administered dose.[18]
- Coadministration of temsirolimus and potent CYP3A4 or CYP3A5 inducers (e.g. rifampicin, dexamethasone, carbamazepine, phenytoin) may reduce sirolimus exposure.[24,25] Concomitant administration of temsirolimus and potent CYP3A4 or CYP3A5 inducers should be avoided, but if an alternative treatment cannot be administered, a dosage adjustment may be necessary.[18]
- Potent inhibitors of CYP3A4 metabolism (e.g. atazanavir, clarithromycin, indinavir, ketoconazole, saquinavir) may increase blood concentrations of sirolimus.[26] If an alternative agent cannot be ad-

ministered, then the temsirolimus dosage may need to be reduced.[18]

- Temsirolimus does not affect CYP2D6 activity; the coadministration of temsirolimus and desipramine, which is metabolized by the CYP2D6 isoenzyme, did not result in clinically relevant changes in the pharmacokinetics of desipramine.[27]

3. Therapeutic Efficacy

The efficacy of temsirolimus in patients with advanced renal cell carcinoma has been investigated in phase I,[11,23] II[21] and III[28] trials. This section will focus on data from randomized multicentre trials (phase II and III) that investigated temsirolimus monotherapy when administered at the recommended dosage of 25 mg once weekly in a 30-minute intravenous infusion (see section 5).[21,28]

Phase II Study

A phase II, randomized, double-blind, multicentre study[21] investigated objective response rates (number of patients with complete response or partial response; primary endpoint) and the time to tumour progression with temsirolimus monotherapy (25 mg [n = 36], 75 mg [n = 38] or 250 mg [n = 37]) administered as a 30-minute intravenous infusion once weekly in patients who had received previous treatment or were considered unsuitable candidates for first-line IL-2 therapy.

- In the intent-to-treat analysis, the objective response rate for patients receiving intravenous temsirolimus 25 mg once weekly was 5.6%, with minor responses experienced by 13.9% of patients. Approximately 53% of patients had complete, partial or minor responses, or stable disease for ≥24 weeks.[21]
- The median time to disease progression was 6.3 months and median survival was 13.8 months.[21]

Phase III Study

A phase III, randomized, open-label, multicentre study[28] investigated the efficacy of temsirolimus in 626 previously untreated patients with histologically or cytologically confirmed metastatic renal cell carcinoma (stage intravenous or recurrent disease) and a poor prognosis. Patients received temsirolimus 25 mg administered once weekly in a 30-minute intravenous infusion (n = 209), a combination of temsirolimus 15 mg administered once weekly in a 30-minute intravenous infusion with IFNα 6 MU administered subcutaneously three times weekly (3 MU for the first week) [n = 210], or IFNα 3 MU (increasing to 18 MU or highest tolerable dose) administered subcutaneously three times weekly (n = 207). Premedication with intravenous diphenhydramine (or similar antihistamine) was given as prophylaxis against an allergic reaction approximately 30 minutes prior to temsirolimus infusion.

Patients included in the study had at least three of the following six indicators of short survival: (i) a serum lactate dehydrogenase level >1.5 times the upper limit of normal; (ii) a haemoglobin level below the lower limit of normal; (iii) a corrected serum calcium level of >10 mg/dL (2.5 mmol/L); (iv) <1 year from initial diagnosis to randomization; (v) a Karnofsky performance score of 60 or 70; or (vi) metastases in multiple organs.[28]

The primary endpoint was the overall survival (based on intent-to-treat analysis). Secondary endpoints included progression-free survival and objective response rates. In addition, quality-adjusted survival data have been presented in an abstract.[29]

Data presented in this section are from the prespecified second interim analysis (446 patients died). The median duration of treatment was 17 weeks in the temsirolimus monotherapy group, 15 weeks for temsirolimus and 12 weeks for IFNα in the combination therapy group, and 8 weeks in the IFNα group.[28]

- Patients receiving temsirolimus alone had a longer median overall survival than recipients of IFNα alone (10.9 vs 7.3 months; figure 1); temsirolimus was associated with a hazard ratio (HR) for death of 0.73 (95% CI 0.58, 0.92; p = 0.008).[28]
- Compared with IFNα alone, a combination of temsirolimus and IFNα did not improve median overall survival time (7.3 months with IFN alone vs 8.4 months with temsirolimus plus IFN; HR 0.96 [95% CI 0.76, 1.20; p = 0.70]).[28]

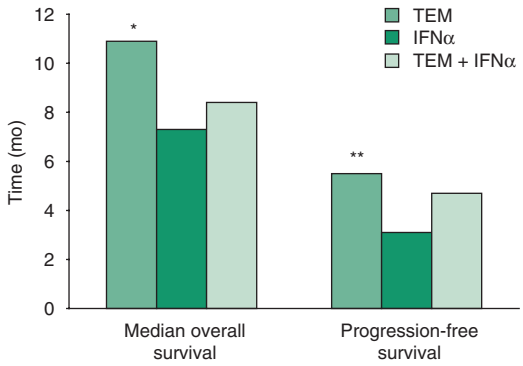


Fig. 1. Efficacy of temsirolimus (TEM). Median overall survival and radiologically assessed progression-free survival in previously untreated patients with advanced renal cell carcinoma receiving TEM 25 mg intravenous once weekly, interferon-α (IFNα) 3–18 MU subcutaneously three times weekly or a combination regimen (TEM + IFNα) of TEM 15 mg intravenous once weekly and IFNα 6 MU subcutaneously three times weekly in a phase III, multicentre clinical study.[18,28] * p = 0.008 vs IFNα, ** p = 0.0001 vs IFNα (not adjusted for multiple comparisons).

- Median progression-free survival times for temsirolimus or the temsirolimus and IFNα combination regimen versus IFNα alone were 5.5 or 4.7 versus 3.1 months (assessed by independent radiological assessment of tumour response) [p = 0.0001 for temsirolimus vs IFNα, not adjusted for multiple comparisons[18]].[28]
- The objective response rates for the temsirolimus alone, combination regimen and IFNα alone treatment groups did not differ significantly (8.6%, 8.1% and 4.8%).[28]
- Patients with renal cell carcinoma treated with temsirolimus alone had significantly greater survival time without symptoms and toxicity than those treated with IFNα alone (see figure 2). Moreover, quality-adjusted survival was longer with temsirolimus than with IFN-α (see figure 2).[29]

4. Tolerability

The tolerability profile of intravenous temsirolimus in patients with advanced renal cell carcinoma and a poor prognosis has been derived from a large, randomized, phase III study comparing the drug with IFNα (see section 3.2 for study design details).[28] Patients (n = 616) who received at least one dose of treatment were included in this analysis.

- The most frequently reported (>30% of patients) adverse events (all grades) with temsirolimus alone were asthenia, rash, anaemia, nausea and anorexia (see figure 3).[28]
- The most common adverse event associated with the IFNα monotherapy was asthenia (64% vs 51% in the temsirolimus group). Grade 3 or 4 asthenia occurred in significantly more IFNα recipients than temsirolimus recipients (26% vs 11%; $p < 0.001$).[28]
- Adverse events (all grades) occurring more commonly in recipients of temsirolimus monotherapy versus the IFNα group included rash (47% vs 6%), hyperlipidaemia (27% vs 14%), peripheral oedema (27% vs 8%), hyperglycaemia (26% vs 11%) [see figure 3], hypercholesterolaemia (24% vs 4%) and stomatitis (20% vs 4%).[28]
- The combination treatment regimen was associated with a higher incidence of anaemia, neutropenia and thrombocytopenia than the IFNα (anae-

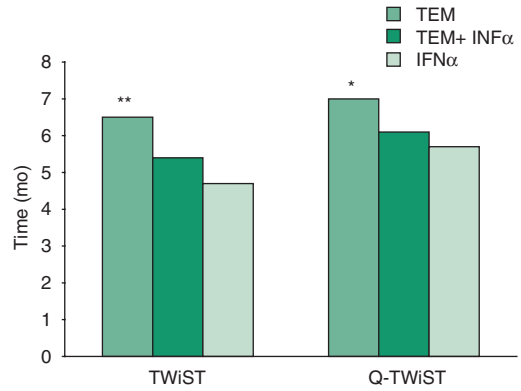


Fig. 2. Comparison of quality-adjusted survival in previously untreated patients with advanced renal cell carcinoma receiving temsirolimus (TEM), interferon-α (IFNα) or combination therapy (TEM + IFNα).[29] Quality-adjusted survival time without symptoms of progression or toxicity (Q-TWiST) was derived from survival times in each of three specified health states (time with serious toxicity, time with progression, and the time without symptoms of progression or toxicity [TWiST]) and patient-reported utility values for those states. Utility values were derived from the European quality-of-life project questionnaire 5D, which was completed at baseline (by 601 of 626 patients), 12 and 32 weeks, and on occurrence of a grade 3 or 4 adverse event (by 230 of 570 patients), progression (by 260 of 300 patients) or early withdrawal. * p = 0.0015, ** p = 0.00048 vs IFNα.[29]

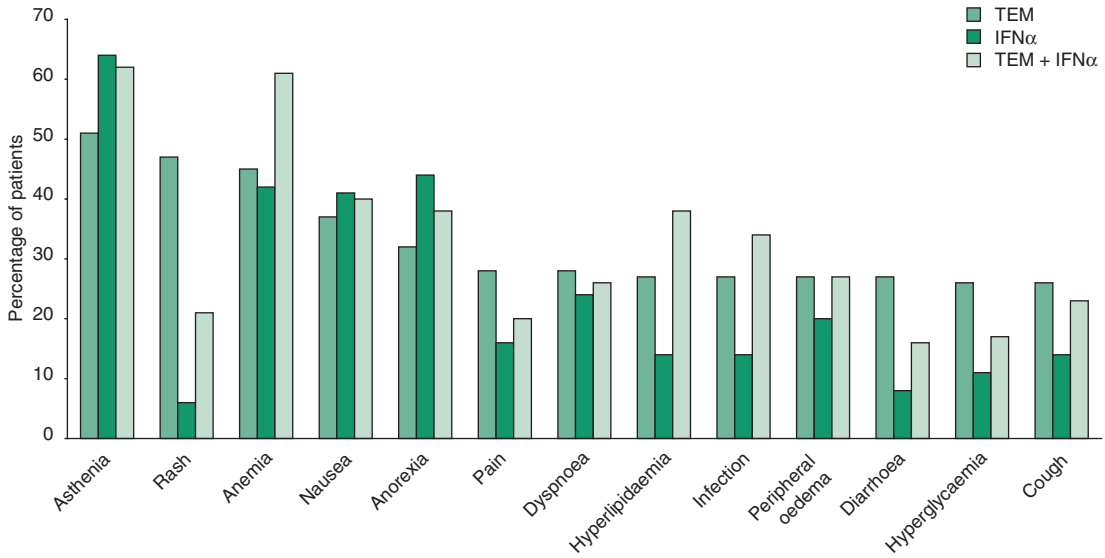


Fig. 3. Tolerability of temsirolimus (TEM) in patients with advanced renal cell carcinoma. The comparative incidence of adverse events occurring in ≥25% of TEM recipients. Patients were randomized to TEM 25 mg intravenous once weekly (n = 208), interferon-α (IFNα) 3–18 MU subcutaneously three times weekly (n = 200) or a combination regimen (TEM + IFNα) of TEM 15 mg intravenous once weekly and IFNα 6 MU subcutaneously three times weekly (n = 208) in a phase III multicentre clinical study.[28]

mia 61% vs 42% [$p < 0.001$], neutropenia 27% vs 12% [$p < 0.001$], thrombocytopenia 38% vs 8% [$p < 0.001$]) or temsirolimus monotherapy groups (anaemia 45% [$p = 0.002$], neutropenia 7% [$p < 0.001$], thrombocytopenia 14% [$p < 0.001$]).[28]

- Grade 3 or 4 adverse events that occurred in >10% of temsirolimus recipients were anaemia (incidence 20%), asthenia and hyperglycaemia (both 11%).[28]
- Significantly fewer grade 3 or 4 adverse events were experienced by temsirolimus monotherapy recipients than by patients receiving IFNα or the combination regimen (67% vs 78% or 87%; $p = 0.02$ for both).[28]
- Withdrawals as a result of adverse events were reported for 7% of temsirolimus, 14% of IFNα and 20% of combination therapy recipients.[28]
- Because of the different frequencies of adverse events in the three groups, dose reductions or delays resulted in differences in the mean relative dose intensities in the three groups.[28] Mean weekly dose intensity was 23.1 mg in the temsirolimus monotherapy group (92% of the planned dose). In the combination group, the mean weekly dose of IFNα was 13.1 MU (72% of the planned dose) and the mean weekly dose of temsirolimus was 10.9 mg (73% of the planned temsirolimus dose). Recipients of IFNα monotherapy received 30.2 MU per week during the first 8 weeks of therapy (≈56% of the planned dose).

5. Dosage and Administration

The currently recommended dose in the US[18] and Europe[25] for temsirolimus in patients with advanced renal cell carcinoma is 25 mg once weekly as an intravenous infusion over 30–60 minutes until disease progression or unacceptable toxicity occurs. Patients should be premedicated with prophylactic intravenous diphenhydramine 25–50 mg (or similar antihistamine) approximately 30 minutes before the initiation of each dose of temsirolimus.[18,25] Local prescribing information should be consulted for more detailed information, including contraindications, precautions, drug interactions and use in special populations.

6. Temsirolimus: Current Status in Advanced Renal Cancer

Temsirolimus is approved in the US[18] for the treatment of patients with advanced renal cell carcinoma, and in Europe[25] for first-line treatment of patients with advanced renal cell carcinoma and at least three of six prognostic risk factors. The drug has shown a significant overall survival benefit and is associated with numerically fewer withdrawals for adverse events compared with standard IFNα therapy in this patient population.

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