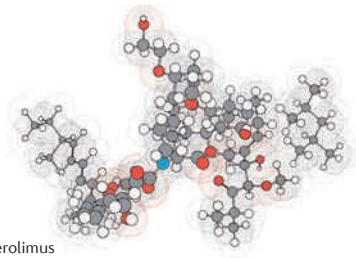
FRESH FROM THE PIPELINE

Everolimus

Michael B. Atkins, Uma Yasothan and Peter Kirkpatrick



Everolimus

In March 2009, everolimus (Afinitor; Novartis), an inhibitor of mTOR, was approved by the US FDA for the treatment of patients with advanced kidney cancer.

Renal cell carcinoma (RCC) accounts for around 2–3% of cancers[1,2]. The primary treatment for RCC is surgical excision, with pharmacotherapy being used in advanced stages of the disease[1,2]. Historically, this involved immunotherapy with interleukin-2 (IL-2) and interferon-α (IFN-α), alone or in combination, but this approach is limited by toxicity and generally poor response rates[1,2].

However, recent advances in the understanding of the molecular biology of RCC — such as the discovery of the key role of vascular endothelial growth factor (VEGF) signalling and related pathways — have brought about a new era of targeted therapy for patients with this disease[2]. Two small molecules that inhibit the kinase activity of VEGF receptors — sorafenib (Nexavar; Onyx/Bayer) and sunitinib (Sutent; Pfizer) — were approved by the FDA for the treatment of advanced RCC in 2005 and 2006, respectively. In addition, the anti-VEGF antibody bevacizumab (Avastin; Genentech/Roche), in combination with IFN-α, was approved in Europe for advanced RCC in 2007. Furthermore, temsirolimus (Torisel; Wyeth), a small-molecule inhibitor of mammalian target of rapamycin (mTOR), a kinase that lies downstream in the phosphatidylinositol 3-kinase (PI3K)–AKT pathway (FIG. 1a), was approved by the FDA for the treatment of advanced RCC in 2007.

Despite these improvements in therapy, most patients with stage IV renal cancer die from disease-related complications at a median of less than 30 months from detection of metastases, and less than 10% of patients survive 5 years[3]. Consequently, there is still a major need for improved treatment options.

Basis of discovery

The PI3K–AKT–mTOR pathway (FIG. 1a) is dysregulated in many cancers[4]. Activation of mTOR promotes the proliferation and survival of tumour cells, and it is also involved in pro-angiogenic signalling pathways in endothelial cells[4].

The natural product rapamycin binds to an intracellular protein known as FK506-binding protein 12 (FKBP12), and the resultant protein–drug complex inhibits the kinase activity of mTOR[4]. Rapamycin has immunosuppressive, antifungal and anticancer activity[4], but its development as an immunosuppressant was prioritized, and it was approved by the FDA for the prevention of transplant rejection in 1999. Multiple derivatives of rapamycin have been synthesized and evaluated with the aim of improving its pharmaceutical properties, and such efforts led to the discovery and development of temsirolimus[5] (which is administered intravenously) for RCC and everolimus[6,7] (which can be orally administered). In 2003, everolimus was approved for the prevention of transplant rejection in Europe, where it is marketed as Certican.

Drug properties

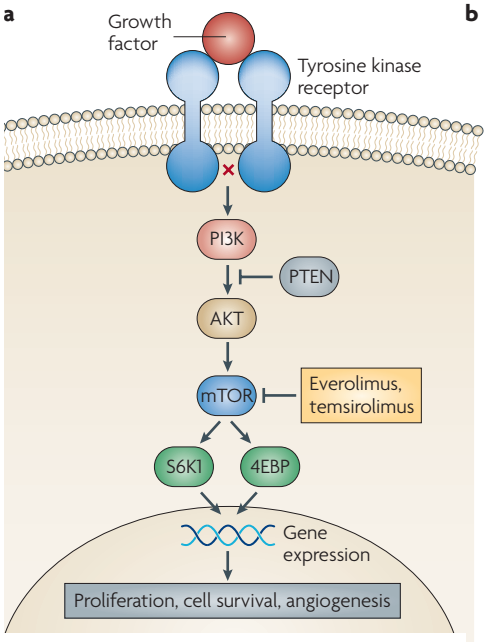
Everolimus (FIG. 1b) binds to FKBP12, forming a complex that inhibits mTOR kinase activity, and reduces the activity of the downstream effectors S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP)[4,6–8]. Everolimus has been shown to inhibit tumour cell proliferation and angiogenesis, with the latter mediated by inhibition of hypoxia-inducible factor 1α (HIF1α) expression[8,9].

Clinical data

The safety and efficacy of everolimus was evaluated in a randomized, double-blind trial involving 416 patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib or both sequentially[8,10]. Prior therapy with bevacizumab, IL-2 or IFN-α was also permitted[8]. The patients were randomized in a 2:1 ratio to receive everolimus (10 mg daily orally) or placebo, both in conjunction with best supportive care[8,10]. The primary endpoint was progression-free survival (PFS), which was assessed by a blinded, independent radiological review[8,10]. In the final analysis, the median PFS for patients in the everolimus group was 4.9 months compared with 1.9 months for patients in the placebo group[8].

Indications

Everolimus is approved by the FDA for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib[8]. ▸



(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-1,18- dihydroxy-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone; $C_{53}H_{83}NO_{14}$; M_r = 958.2

Figure 1 | **Selected signalling pathways and drugs for RCC. a** | A simplified overview of the PI3K–AKT–mTOR pathway, together with points of action of drugs for RCC. **b** | Everolimus.

ANALYSIS | RENAL CELL CARCINOMA

Analysing issues in the treatment of RCC is Michael B. Atkins, M.D., Professor of Medicine at Harvard Medical School and Leader, Renal Cancer Program, Dana-Farber/Harvard Cancer Center, Boston, USA.

A recent Cambridge Consensus Conference identified five research priorities to tackle the critical obstacles to the successful treatment of patients with RCC[11]. In order of importance, the first is determination of the mechanisms of acquired resistance to VEGF-targeted therapy, which will probably involve the study of key signalling pathways used by RCC cells to adjust to the loss of VEGF signalling. Second is the identification of new targets (particularly those within the tumour) followed by testing inhibitors of those targets in defined patient populations. Third is identification of predictive and surrogate biomarkers, which will help select patients for particular therapies and provide early information on treatment efficacy. Fourth is exploration of combination versus sequential therapy with the aim of determining the most beneficial approach for patients with RCC. Fifth is the determination of mechanisms of response to current agents, with a particular emphasis on how this might lead to the development of more effective agents and more rational treatment sequencing.

The recent approval of everolimus provides an opportunity to address some of these issues. The activity of everolimus in patients with resistance to sunitinib or sorafenib suggests that the mTOR pathway might contribute to the acquired resistance to VEGF pathway blockade. However, it remains to be determined whether sustained blockage of the VEGF pathway in combination with mTOR pathway inhibition might be superior to mTOR inhibition alone. Furthermore, mTOR pathway inhibitors as initial therapy might improve the outcome for some patients. Identifying tumour-based molecular markers, such as S6K1 or AKT activation status, that could help predict preferential sensitivity to mTOR inhibition over either VEGF pathway inhibition or immunotherapy is a focus of active investigation. In addition, the value of functional imaging (PET scans) to provide early information regarding effectiveness and potentially onset of resistance to mTOR pathway inhibition is also currently being studied. Even in patients in which mTOR inhibition and VEGF pathway inhibition are both effective, it is conceivable that quality of life might be superior if the potentially less toxic mTOR inhibitor is provided as initial therapy. Alternatively, the combination of an mTOR inhibitor and a VEGF pathway inhibitor might produce better tumour shrinkage and longer PFS than either agent used alone. Although promising, such 'horizontal' combinations will probably need to be significantly better than the single agents used in sequence to justify the added toxicity and cost that is associated with the extended use of two agents. Finally, mTOR inhibitors such as everolimus, because of their tolerability and unique mechanism of action, may offer benefit in the adjuvant setting relative to observation or even VEGF pathway inhibitors.

Of note, mTOR inhibition represents the first effective tumour-targeted treatment approach in RCC; however, the mechanisms underlying this effect remain uncertain. For example, it is unclear to what extent the therapeutic benefit is mediated by anti-angiogenic effects, perhaps by diminished HIF-1 production, compared with direct effects on cell proliferation mediated by mTOR inhibition. The modest activity of everolimus and other rapamycin analogues in RCC suggests that there may be additional benefit for targeting more proximal components of the PI3K–AKT pathway. Nevertheless, the activity of mTOR inhibitors such as everolimus in patients with RCC serves to heighten the enthusiasm for identifying and exploring additional tumour-specific targets for this disease.

Box 1 | The market for RCC

Analysing the market for RCC is Uma Yasothan, IMS Health, London, UK.

Several new targeted drugs for RCC — sunitinib (Sutent; Pfizer), sorafenib (Nexavar; Bayer/Onyx) and temsirolimus (Torisel; Wyeth) — have recently been approved in the United States. In 2008, sunitinib and sorafenib (which have been approved for RCC as well as other cancer indications) had sales of €622 million and €344 million, respectively, with strong year-on-year growth of 28% and 62%, respectively[12]. Temsirolimus, an injectable mTOR inhibitor that was approved for RCC ~1.5 years after sorafenib and sunitinib, had 2008 sales of €78 million[12].

In March 2009, everolimus (Afinitor; Novartis), an oral mTOR inhibitor, was approved by the FDA for the treatment of advanced RCC in patients who have failed to respond to sunitinib or sorafenib. Its pivotal study was halted early when initial results showed that everolimus more than doubled progression-free survival compared with placebo[10].

In Europe, everolimus (marketed as Certican) is approved for the prevention of organ rejection following heart or kidney transplantation, and had 2008 sales of €55 million for this indication[12]. In May 2009, everolimus was granted a positive recommendation for approval in the EU for the treatment of RCC. Although RCC is a market with considerable unmet medical need, the major market potential for everolimus is anticipated to be from other cancer indications, including gastric and breast cancers, tuberous sclerosis complex, lymphoma, liver cancer and neuroendocrine tumours, for which the product is in late-stage clinical trials. Analysts estimate that everolimus could have peak sales of US$364 million in 2015 (REF. 13).

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Competing financial interests
M.B.A declares competing financial interests: see web version for details.