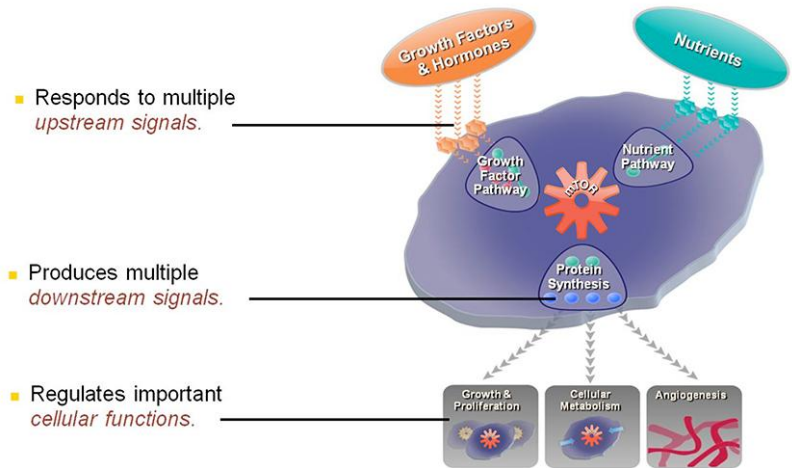


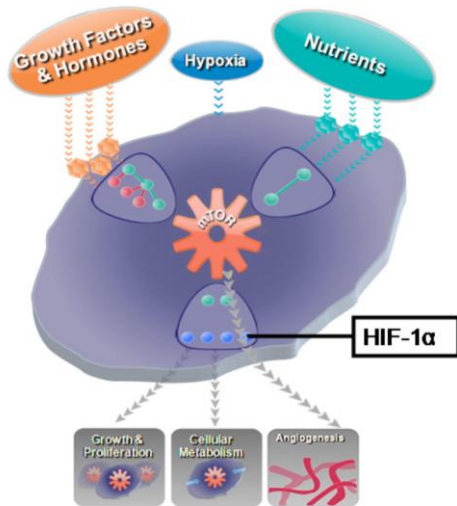
mTOR INHIBITION IN RENAL CELL CARCINOMA

The Role of mTOR in a Normal Cell

Located inside the cell, mTOR is a protein that is responsible for regulating important growth factors and signaling pathways that control basic cell functions, including cell growth, cellular metabolism and the creation of new blood vessels through angiogenesis.



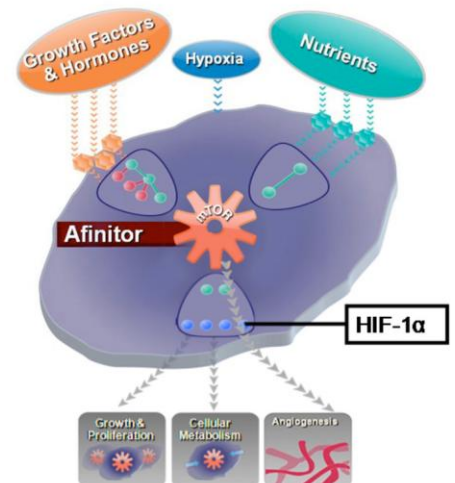
Increased Activity of mTOR in a Cancer Cell



In renal cell carcinoma, overactivation of some signaling pathways may lead to increased mTOR activity, resulting in uncontrolled cell growth, increased cellular metabolism, the creation of new blood vessels and ultimately cancer progression.

mTOR Inhibition in Renal Cell Carcinoma

Afinitor® (everolimus) tablets, an mTOR inhibitor, blocks mTOR and prevents some signals inside the cell from contributing to cell growth, cellular metabolism and the creation of new blood vessels. As a result, tumor growth may be slowed or halted.



About Afinitor

Afinitor is the first oral, daily therapy (5 mg and 10 mg tablets) to treat advanced kidney cancer after failure of treatment with Sutent[®] (sunitinib)* or Nexavar[®] (sorafenib)**. In cancer cells, Afinitor continuously targets mTOR, a protein that acts as a central regulator of tumor cell division, blood vessel growth and cell metabolism. Afinitor is also being studied in multiple cancer types, including neuroendocrine, breast, gastric and hepatocellular carcinoma (HCC), as well as tuberous sclerosis complex (TSC) and non-Hodgkin's lymphoma.

The active ingredient in Afinitor is everolimus, which is available in different dosage strengths under the trade name Certican[®] for the prevention of organ rejection in heart and kidney transplant recipients. Certican was first approved in the EU in 2003. Certican is not approved for use in the US.

Important safety information

Afinitor is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives or to any of the excipients. Potentially serious adverse reactions include non-infectious pneumonitis and infections for which patients should be monitored carefully and treated as needed. In addition, non-infectious pneumonitis may require temporary dose reduction and/or interruption or discontinuation. Patients with systemic invasive fungal infections should not receive Afinitor. Oral ulceration is a common side effect with Afinitor. Renal function, blood glucose, lipids and hematological parameters should be evaluated prior to the start of therapy with Afinitor and periodically thereafter. Strong or moderate CYP3A4 or P-glycoprotein inhibitors should be avoided. An increase in the dose of Afinitor is recommended when co-administered with a strong CYP3A4 inducer. Live vaccinations and close contact with those who have received live vaccines should be avoided. Afinitor should not be used in patients with severe hepatic impairment. Afinitor may cause fetal harm in pregnant women.

The most common adverse reactions (incidence $\geq 30\%$) were stomatitis, infections, asthenia, fatigue, cough and diarrhea. The most common grade 3/4 adverse reactions (incidence $\geq 3\%$) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain and asthenia. The most common laboratory abnormalities (incidence $\geq 50\%$) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence $\geq 3\%$) were lymphopenia, hyperglycemia, anemia, hypophosphatemia and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed for patients receiving Afinitor.

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* Sutent[®] is a registered trademark of Pfizer Inc.

** Nexavar[®] is a registered trademark of Bayer HealthCare Pharmaceuticals, Inc. and Onyx Pharmaceuticals.