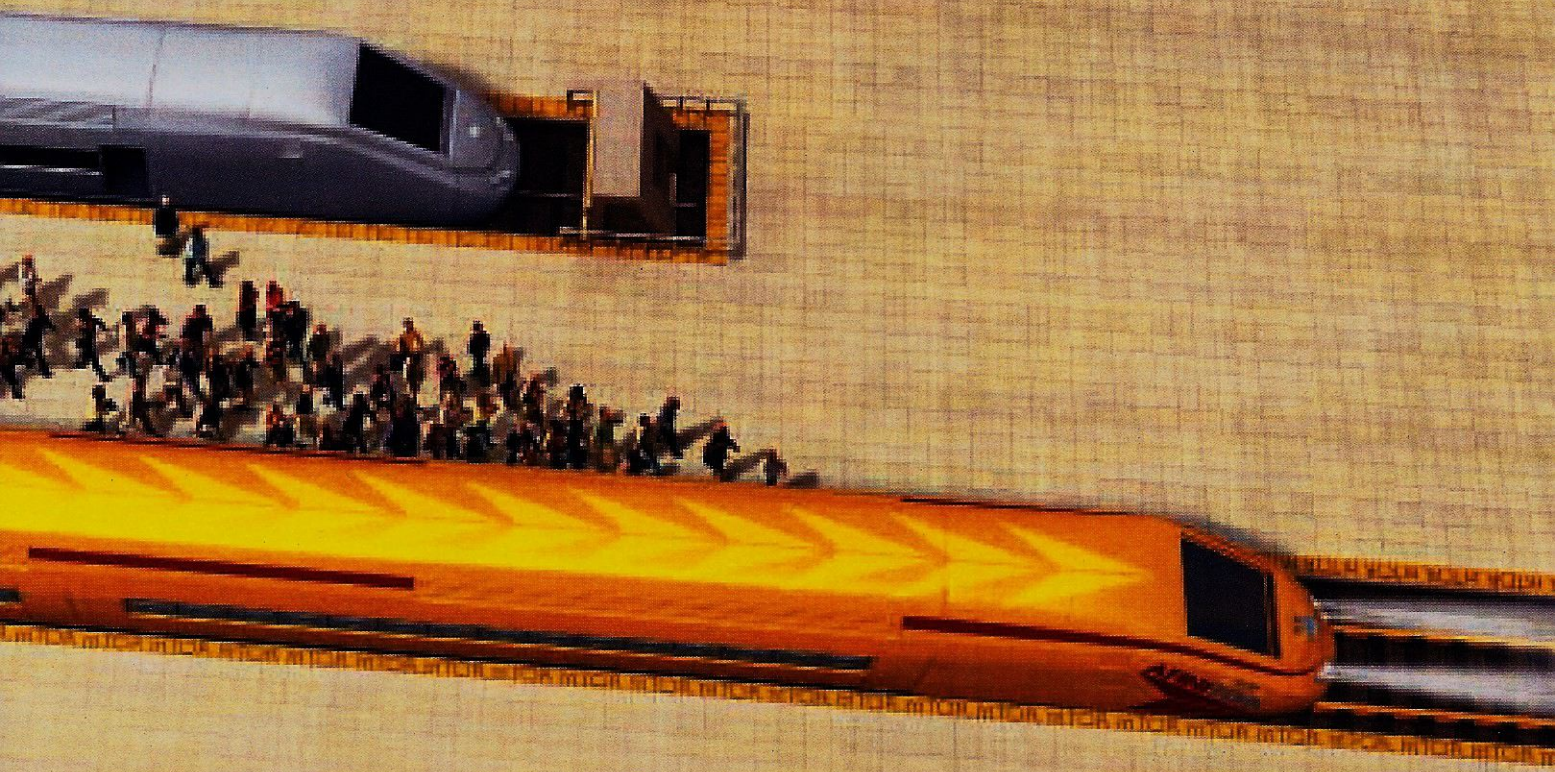
DRAFT: All data based on proposed label and subject to change pending review and comment by Health Authority.

In advanced RCC:



New AFINITOR—

Proven Efficacy When a VEGF-Targeted Therapy Fails

Powered by Phase III evidence, AFINITOR, a new oral mTOR inhibitor, is proven to more than double median progression-free survival vs placebo after sunitinib or sorafenib failure in advanced renal cell carcinoma (RCC).[1-3]

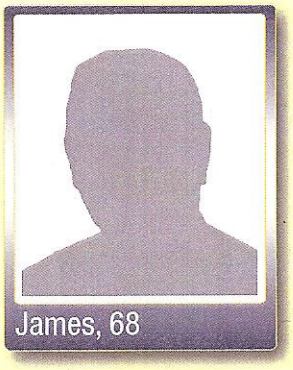
NEW AFINITOR® (everolimus) Tablets

Switch tracks

AFINITOR is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

RCC patient who presents with synchronous metastatic disease and develops progressive disease on sunitinib therapy

History



- A 68-year-old male ex-smoker with an unremarkable medical history
- Developed left flank pain and weight loss of 7 kilograms over the last 6 months (Karnofsky Performance Status 80)
- Was seen by his internist who noted a nontender mass in the left upper quadrant and obtained the following examinations:

— Laboratory studies

- WBC: 7.6 x $10^3/\mu L$
- Hb: 14.5 g/dL (Lower Limit of Normal=14.0 g/dL)
- Corrected calcium: 9.8 mg/dL
- Platelets: 309 x $10^3/\mu L$
- Serum creatinine: 1.0 mg/dL
- LDH: 300 U/L (Upper Limit of Normal=625)

— Imaging studies

- Chest X-ray: bilateral subcentimeter pulmonary nodules
- CT chest: multiple bilateral lung lesions (largest 1.5 cm)
- CT abdomen/pelvis: 8-cm mass on the left kidney
- Bone scan: increased uptake in several ribs and thoracic vertebrae consistent with skeletal metastases

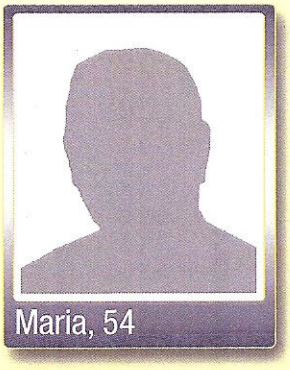
Treatment

- A diagnosis of advanced metastatic RCC was made, and the patient was referred to a urologist who performed a cytoreductive nephrectomy. The pathology report indicated an 8.5-cm clear cell RCC, Fuhrman Grade 3/4
- MSKCC* prognostic risk category: intermediate
- Patient was referred to a medical oncologist and was started on sunitinib (50 mg PO QD, 4 weeks on, 2 weeks off). During week 4 of cycle 1, the patient developed severe fatigue that prevented normal daily activities (Grade 3). Dose reduction to 37.5 mg QD 4/6 weeks was required in subsequent cycles
- Best response was stable disease with minimal regression of several pulmonary nodules
- After 11 months of therapy, a CT scan of the chest showed several new lung and liver lesions, and sunitinib was discontinued

Clinical status and implications

- Progression of disease on sunitinib requires reevaluation of James' status
- The treatment of advanced RCC has evolved, and effective options for patients with disease refractory to kinase inhibitors such as sunitinib now exist
- A recent Phase III trial provides evidence of PFS prolongation by everolimus after progression on a VEGF†-targeted agent such as sunitinib[1]

Patient with progressive metastatic RCC after sequential therapy with IFN-α followed by sorafenib



History

- A 54-year-old nonsmoking female with a history of mild hypertension that has been medically managed for 3 years
- She noted several episodes of painless gross hematuria and was seen by a urologist. A 5.5-cm right renal mass was found on an abdominal CT scan, and a subsequent right nephrectomy was performed

  Pathology: 5.5-cm clear cell carcinoma, Fuhrman Grade 2/4 with capsular invasion; no lymph nodes identified ($T_3N_XM_0$).
- Seen in follow-up every 6 months for 2 years. Four years postnephrectomy, she developed a chronic nonproductive cough and was seen by her internist. A physical examination was unremarkable (Karnofsky Performance Status 90), but a routine chest X-ray revealed enlarged right hilar lymph nodes and 4 bilateral pulmonary nodules (largest 3.0 cm). Studies obtained included the following:
  - — Laboratory studies
    - WBC: 8.65 x 10^3/μL
    - Platelets: 286 x 10^3/μL
    - Corrected calcium: 9.2 mg/dL
    - Serum creatinine: 0.9 mg/dL
    - Hb: 12.5 g/dL (Lower Limit of Normal=12.0 g/dL)
    - LDH: 350 U/L (Upper Limit of Normal=625)
  - — Imaging studies
    - CT chest: bilateral pulmonary nodules (largest 3.2 cm), right hilar adenopathy
    - CT abdomen/pelvis: previous right nephrectomy; no evidence of metastatic disease
    - CT brain: no evidence of metastatic disease
    - Bone scan: no evidence of skeletal metastases
  - — Bronchoscopy and needle biopsy: consistent with clear cell RCC

Treatment

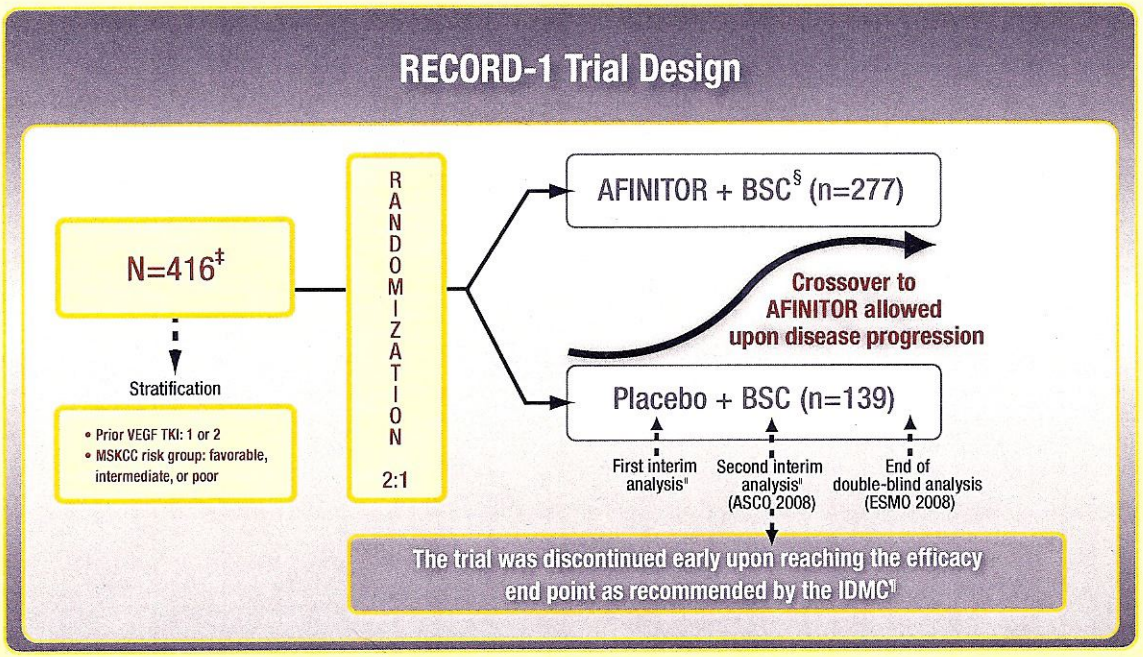
- A diagnosis of metastatic RCC was made
- MSKCC* prognostic risk category: favorable
- The patient was treated with interferon-α (IFN-α) (9.0 million units 3 times/week) subcutaneous for 24 weeks. Toxicity included Grade 3 fatigue, chills, and fever, and required dose reduction and delays
- Repeat CT scans of the chest/abdomen (week 24) demonstrated stable pulmonary nodules, and several 1.0-cm enhancing liver lesions consistent with new metastases
- After 6 months of IFN-α therapy, the patient was considered to have progressive disease, and additional treatment was considered. Sorafenib 400 mg BID PO was then initiated. Toxicity included Grade 2 hand-foot syndrome and mild diarrhea. Her BP also increased to 178/115 and required more aggressive management. Dose reduction of sorafenib (400 mg QD) was also required
- Follow-up CT scans of the chest/abdomen at 3 months demonstrated stable disease with 15% decrease in several pulmonary nodules and central necrosis in the right hilar mass
- Best response was stable disease
- After 6 months of sorafenib therapy, CT scans showed stable pulmonary lesions but progressive disease in the liver with several new lesions noted, and sorafenib was discontinued

Clinical status and implications

- Progression of disease after IFN-α and subsequently sorafenib requires reevaluation of Maria's status
- The treatment of advanced RCC has evolved, and effective options for patients with disease refractory to kinase inhibitors such as sorafenib now exist
- A recent Phase III trial provides evidence of PFS prolongation by everolimus after progression on a VEGF†-targeted agent such as sorafenib[1]

New AFINITOR delivers the next level of evidence

The AFINITOR pivotal trial is the first Phase III, prospective, randomized, double-blind, placebo-controlled trial to demonstrate a clinical benefit after sunitinib or sorafenib failure[1]



- 74% of patients were previously treated with only one VEGF TKI (sunitinib or sorafenib)[1]
- Previous therapy with bevacizumab, interleukin 2, or interferon alfa was also permitted[1]
- Upon disease progression, 88% of placebo patients crossed over to AFINITOR[4]

*MSKCC=Memorial Sloan-Kettering Cancer Center.
† VEGF TKI=vascular endothelial growth factor tyrosine kinase inhibitor.
‡ Enrollment criteria for the study: Patients with progressive disease on or within 6 months of prior sunitinib or sorafenib treatment; histological or cytological evidence of clear-cell component of advanced RCC.
§ Best supportive care.
‖ Interim analyses planned after ≈ 30% and 60% of targeted 290 events.[1]
¶ Independent Data Monitoring Committee.

AFINITOR is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Please see Summary of Product Characteristics in pocket.
Please see Important Safety Information on page 11.

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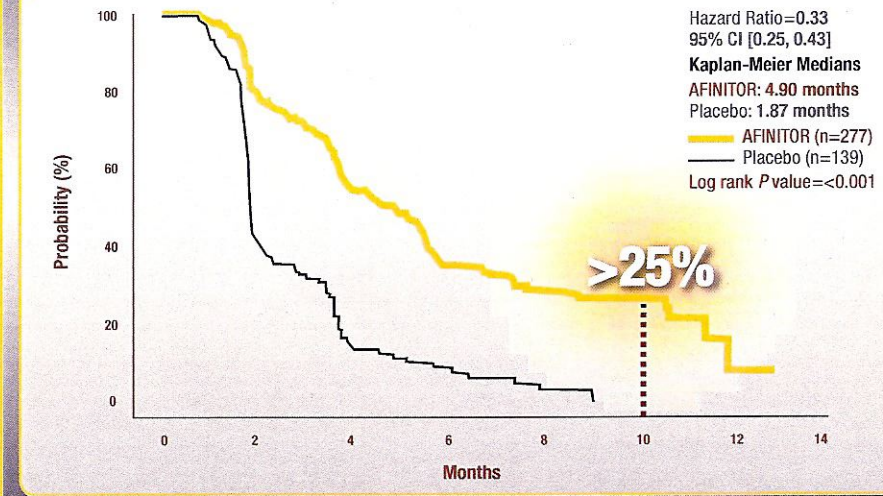
NEW AFINITOR® (everolimus) Tablets

Switch tracks

New AFINITOR more than doubled median PFS after a VEGF-targeted therapy failure[3]

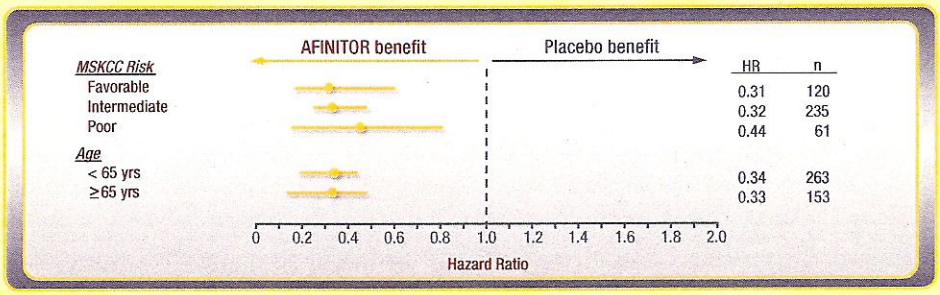
Patients had a >25% probability of being progression free at 10 months with AFINITOR based on Kaplan-Meier[2]

Progression-free survival by treatment evaluated by a blinded Independent Central Review Board[2,3]



- AFINITOR demonstrated a **67%** reduction in the relative risk of progression or death as compared with placebo[4]

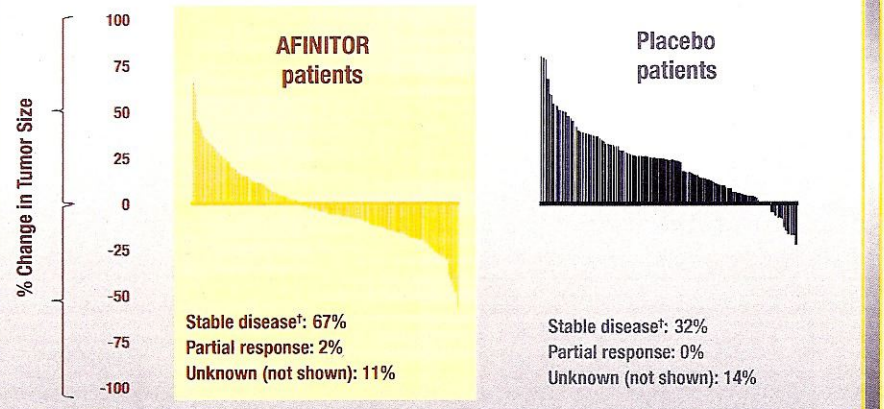
AFINITOR provided treatment benefit for all MSKCC risk and age groups[2,4]



New AFINITOR—Proven to deliver clinical benefit

AFINITOR demonstrated a clinical benefit* rate of 69%[4]

Maximum % change in target lesions and objective response rate[2] (independent radiological review)



"[AFINITOR] should now be considered as the standard-of-care in patients with metastatic renal cell carcinoma whose disease has progressed after treatment with [VEGF] targeted therapies."

—Motzer et al. *Lancet.* 2008.[1]

*Clinical benefit (no progressive disease) refers to stable disease + partial response + complete response (SD + PR + CR).[5]

† Stable disease was defined as disease that remained unchanged for at least 56 days (neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease). Tumor response was evaluated by independent radiological review according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Efficacy evaluations were performed every 8 weeks.[1]

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NEW AFINITOR® (everolimus) Tablets

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AFINITOR demonstrated a low incidence of severe laboratory abnormalities

Low rate of Grade 3/4 laboratory abnormalities reported with AFINITOR[2]

Key laboratory abnormalities considered as adverse reactions and reported at a higher rate in the AFINITOR arm than the placebo arm[2]

	AFINITOR 10 mg/day (n=269)			Placebo (n=135)		
Laboratory parameter	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hematology[§]						
Hemoglobin decreased	91	9	<1	76	5	0
Lymphocytes decreased	42	14	2	29	5	0
Platelets decreased	20	<1	0	2	0	<1
Neutrophils decreased	11	0	0	3	0	0
Clinical chemistry						
Cholesterol increased	76	3	0	32	0	0
Triglycerides increased	71	<1	0	30	0	0
Glucose increased	50	12	0	23	2	0
Creatinine increased	47	<1	0	33	0	0
Phosphate decreased	32	5	0	7	0	0
Aspartate transaminase (AST) increased	21	<1	0	7	0	0
Alanine transaminase (ALT) increased	18	<1	0	4	0	0
Bilirubin increased	2	<1	<1	2	0	0

CTCAE Version 3.0

[§] Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, and thrombocytopenia.

Renal function

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.[4] In the Phase III clinical trial, only patients with adequate renal function were enrolled (serum creatinine $\leq$1.5 x ULN).

Blood glucose

Hyperglycemia has been reported in clinical trials. The majority of cases occurred in patients who had an abnormal fasting glucose level before taking AFINITOR. Monitoring of fasting serum glucose is recommended prior to the start of AFINITOR therapy and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on AFINITOR.[4]

Hematological parameters

Decreased hemoglobin, neutrophils, and platelets have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.[4]

AFINITOR is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

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New AFINITOR is generally well tolerated when a VEGF-targeted therapy fails[2,4]

- Only 7% of patients discontinued treatment due to adverse reactions[4]
- AFINITOR patients received an average of 92% of the planned dose during the trial[4]

Low rate of Grade 3/4 adverse reactions reported with AFINITOR[2,4]

Treatment-related adverse reactions reported in at least 5% of patients and at a higher rate in the AFINITOR arm than in the placebo arm[2,4]

	AFINITOR 10 mg/day (n=274)			Placebo (n=137)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any adverse reaction	89	35	3	58	7	0
Nervous system disorders						
Dysgeusia	10	0	0	2	0	0
Headache	9	0	0	5	0	0
Infections and infestations						
Infections*	13	2	2	2	0	0
Metabolism and nutrition disorders						
Anorexia	19	<1	0	6	0	0
Respiratory, thoracic, and mediastinal disorders						
Cough	14	0	0	4	0	0
Pneumonitis*†	14	4	0	0	0	0
Epistaxis	12	0	0	0	0	0
Dyspnea	10	2	0	3	0	0
Gastrointestinal disorders						
Stomatitis‡	44	4	<1	8	0	0
Diarrhea	21	2	0	4	0	0
Nausea	18	<1	0	8	0	0
Mucosal inflammation	17	1	0	2	0	0
Vomiting	15	<1	0	4	0	0
Dry mouth	6	0	0	4	0	0
Skin and subcutaneous tissue disorders						
Rash	28	1	0	5	0	0
Dry skin	12	<1	0	4	0	0
Pruritus	12	<1	0	3	0	0
General disorders and administration site conditions						
Fatigue	23	3	0	17	<1	0
Asthenia	22	2	0	10	<1	0
Edema peripheral	13	<1	0	4	0	0
Pyrexia	6	0	0	2	0	0

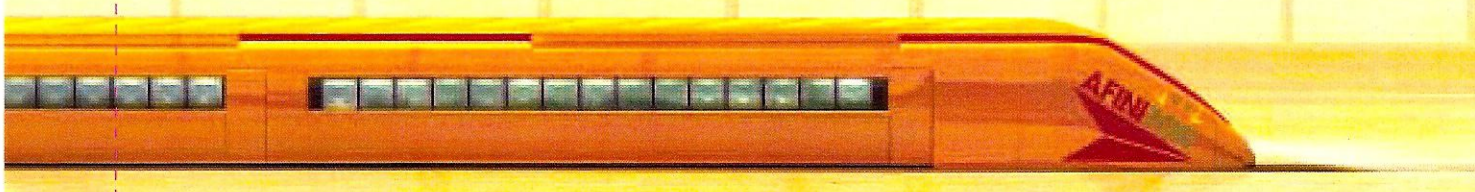
Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

* All infections reported including pneumonia, aspergillosis, candidiasis, and sepsis.

† Includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, and pulmonary toxicity.

‡ Stomatitis (including aphthous stomatitis) and mouth ulceration.

- The majority of the cases of pneumonitis were reversible with drug interruption and medical management[4]



In advanced RCC, when a VEGF-targeted therapy fails

AFINITOR—The once-daily, oral therapy

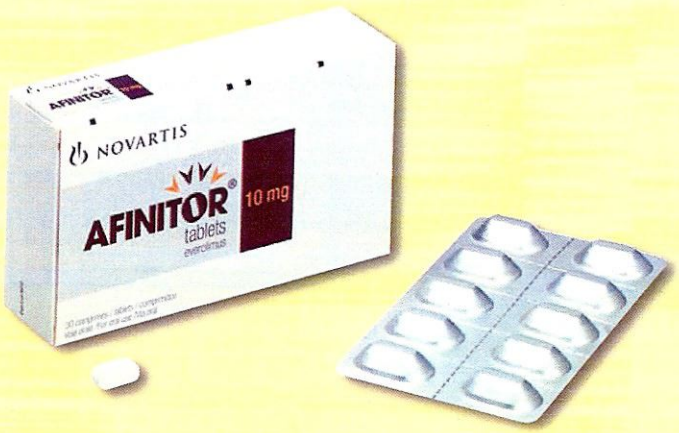
Simple dosing regimen is convenient for patients

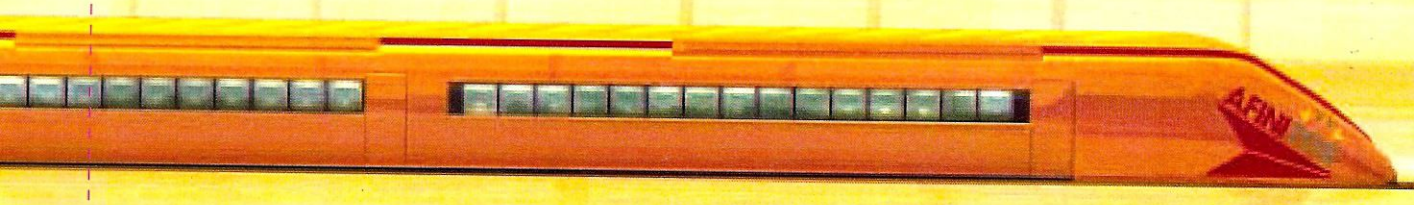
- AFINITOR is available in 10-mg and 5-mg once-daily tablets[1,6]

AFINITOR is easy to administer[6]

- Dosage is the same regardless of age, gender, body weight, or renal function
- No premedication is required
- Take once daily in a fasting state or after a light, fat-free meal

One 10-mg tablet, once a day

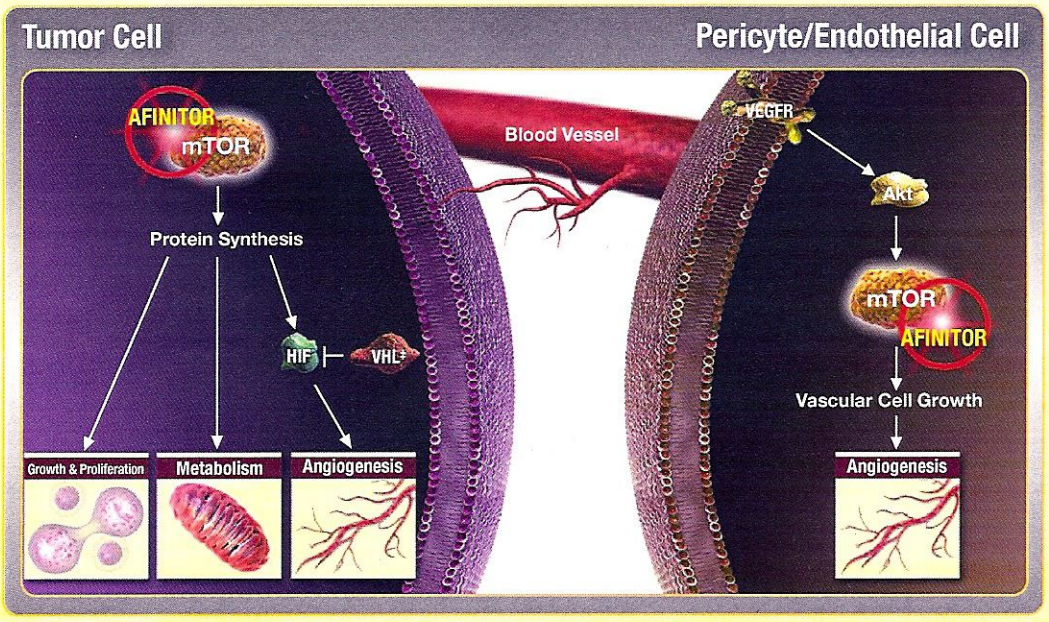




AFINITOR is the only oral mTOR* inhibitor

AFINITOR inhibits mTOR—a central cellular regulator in both tumor cells and endothelial cells[6-11]

- The intracellular kinase mTOR plays a key role in many different pathways important in RCC[7]
  —Affected pathways are both upstream of HIF† and downstream of VEGF



AFINITOR inhibits mTOR, resulting in:

- Reduced tumor cell growth and proliferation[6,7]
- Decreased tumor angiogenesis[6-8]
- Inhibited cell metabolism[10,11]

VEGF-targeted therapies primarily inhibit only angiogenesis

*mTOR=mammalian target of rapamycin.
†HIF=hypoxia-inducible factors.
‡VHL=Von Hippel-Lindau tumor suppressor protein.

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In advanced RCC, when a VEGF-targeted therapy fails

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Take the AFINITOR track

"[AFINITOR] should now be considered as the standard-of-care in patients with metastatic renal cell carcinoma whose disease has progressed after treatment with [VEGF] targeted therapies."
—Motzer et al. *Lancet.* 2008.[1]

- AFINITOR is the only therapy with Phase III evidence after a VEGF-targeted therapy failure
  - —More than doubled median progression-free survival (PFS) from 1.87 to 4.9 months[3]
  - —Patients had a >25% probability of being progression free at 10 months based on Kaplan-Meier[2]
  - —67% reduction in risk of disease progression or death achieved across all MSKCC patient subgroups ($P<0.001$)[4]
- Generally safe and well tolerated with a low discontinuation rate[4,6]
- Convenient, once-daily, oral mTOR inhibition[4,6]

AFINITOR is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

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