


Targeted Molecular Therapy for Renal Cell Carcinoma: Impact on Existing Treatment Paradigms

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RCC: Incidence

New Cancer Cases Expected in the U.S. During 2009

Prostate	192,280	25%		Breast	192,370	27%
Lung & bronchus	116,090	15%		Lung & bronchus	103,350	14%
Colon & rectum	75,590	10%		Colon & rectum	71,380	10%
Urinary bladder	52,810	7%		Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%		Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%		Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%		Thyroid	27,200	4%
Leukemia	25,630	3%		Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%		Ovary	21,550	3%
Pancreas	21,050	3%		Pancreas	21,420	3%
All Sites	766,130	100%	All Sites	713,220	100%	

- Median age at diagnosis: 64 yrs
- Incidence is increasing 2.5% per yr
- Estimated diagnoses of men and women in 2009: 57,760

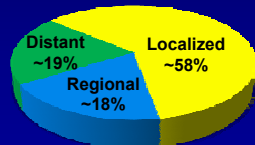
RCC=renal cell carcinoma.

Jemal. *CA Cancer J Clin.* 2009;59:228; National Cancer Institute website. SEER Cancer Statistics Review, 1975-2006. http://seer.cancer.gov/csr/1975_2006/index.html. Accessed 10/6/09; Lam. *Clin Cancer Res.* 2004;10:6304s.

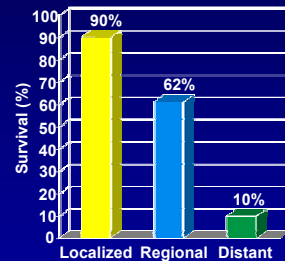
RCC: Prognosis

- RCC is often diagnosed in the advanced stages
- 12,980 deaths projected for 2009
- Historically, median survival for mRCC: 10-13 mo

Distribution of Stage at Diagnosis*



5-Year Relative Survival Rate by Stage at Diagnosis (1999-2005)



*Stage categories do not total 100% because sufficient information was not available to assign a stage to all cancer cases.

mRCC=metastatic renal cell carcinoma.

Jemal. *CA Cancer J Clin.* 2009;59:228; National Cancer Institute website. SEER Summary Staging Manual 2000. <http://seer.cancer.gov/tools/ssml/>. Accessed 10/6/09; Lam. *J Clin Oncol.* 2006;24:5565.

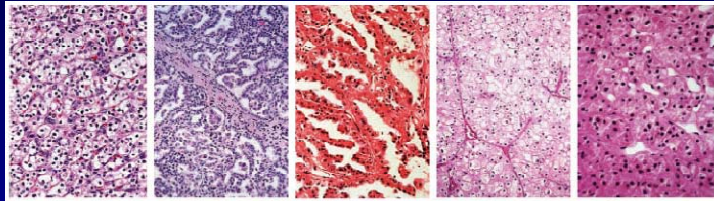
MSKCC and CCF Poor Risk Factor Criteria for Advanced RCC

MSKCC Criteria 2002		CCF Criteria 2005	
KPS	<80	Time From Diagnosis to Treatment With IFN- α	<12 mo
Time From Diagnosis to Treatment With IFN- α	<12 mo	Hemoglobin	<LLR
Hemoglobin	<LLR	Corrected Serum Calcium	>10.0 mg/dL
LDH	>1.5 x ULR	LDH	>1.5 x ULR
Corrected Serum Calcium	>10.0 mg/dL	Prior Radiotherapy	Yes
MSKCC Criteria 2004		Presence of Hepatic, Lung, or Retroperitoneal Lymph Node Metastases	Yes
KPS	<80%		
Hemoglobin	\leq 13 g/dL (men) or \leq 11.5 g/dL (women)		
Corrected Serum Calcium	\geq 10.0 mg/dL		

KPS=Karnofsky performance status; LDH=lactate dehydrogenase; LLR=lower limit of laboratory's reference range; ULR=upper limit of laboratory's reference range.

Motzer. *J Clin Oncol.* 2002;20:289; Motzer. *J Clin Oncol.* 2004;22:454; Mekhail. *J Clin Oncol.* 2005;23:832.

RCC: Histologic Subtypes



Type	Clear Cell	Papillary Type 1	Papillary Type 2	Chromophobe	Oncocytoma
Frequency	75%	5%	10%	5%	5%
Gene	VHL	c-Met	Fumarate hydratase	Birt Hogg Dubé	Birt Hogg Dubé

VHL= von Hippel-Lindau.

Reproduced with permission from Linehan. *J Urol.* 2003;170:2163.

History: Treatment of metastatic renal cancer

- 1980 – No effective therapy for RCC
 - Vinblastine (chemotherapy)
 - Megace (hormonal therapy)
- 1987 – Immunotherapy
 - Agents that activate the immune system against cancer
 - Interferon-alpha
 - Interleukin 2 (IL-2)
- 2004 – Signaling inhibitors (modern era)
 - VEGF pathway inhibitors
 - mTOR inhibitors
- 2010 – Plethora of choices!

Immunotherapy

- Uses natural substances to boost patients' natural defenses against cancer (also called biologic therapy)
- Due to lack of effective treatment in 1980's, immunotherapy was tested in kidney cancer

Interferon-alpha

- Made by body to fight virus infections
 - Increases activation of white blood cells
 - Makes tumor more visible to immune system
 - Slows cancer cell growth
- Injection into skin or intravenously produced responses in some cancers
- Tested in metastatic renal cancer

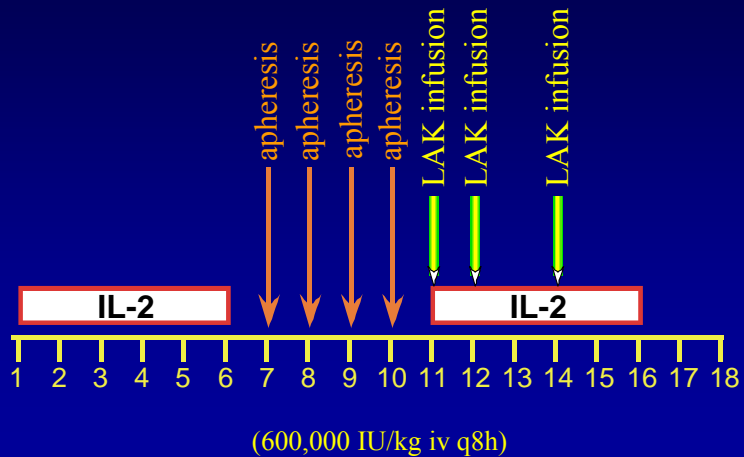
Interferon-alpha

- Early studies in renal cancer suggested that about 20-25% of patients responded
 - Required chronic administration
 - “Flu-like” symptoms bothersome
 - Average duration of effectiveness short
 - Complete or long-term remissions of cancer rare
 - Became “community standard” treatment for RC

Interleukin-2

- Activates T cells (in presence of Ag)
 - proliferation-(expansion)
 - cytotoxicity-(cancer cell killing)
- Activation of LAK cells
- Cytokine “storm”
 - TNF
 - IL-1
 - IFN γ

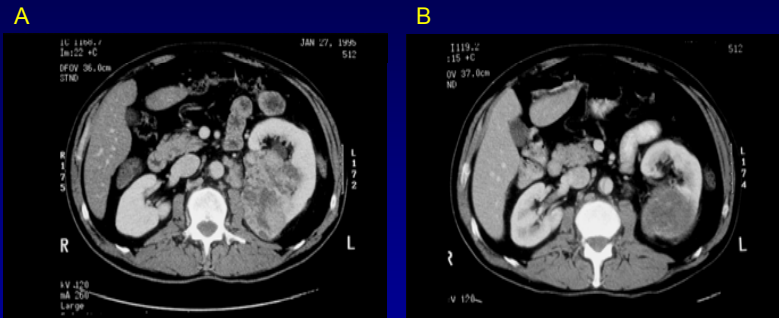
IL-2 treatment protocol



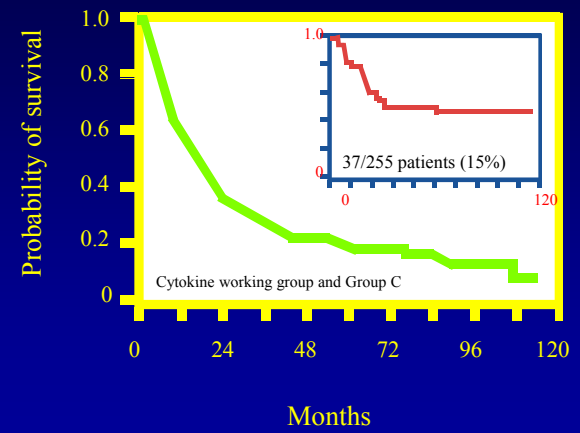
Side effects of IL-2

- 1) Required a specialized center
- 2) Hypotension
- 3) "Vascular leak syndrome"
 - a) reversible changes in kidney function
 - b) fluid retention (20 lbs)
 - c) lung congestion
 - d) temporary changes in brain function

Why use IL-2



Long term follow-up of IL-2 in renal cancer

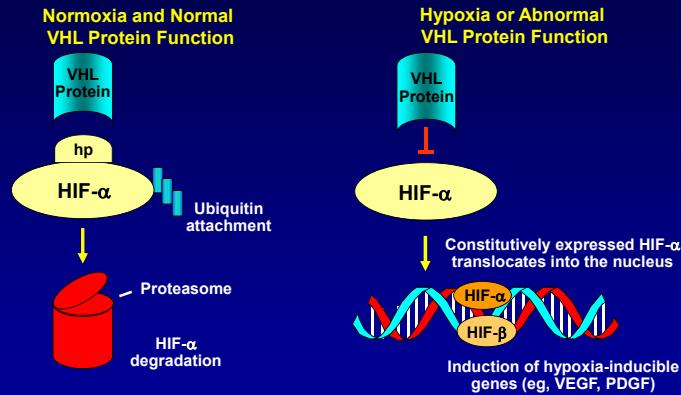


Who benefits from IL-2

- Patients with 100% performance status
- Conventional clear cell type cancer
- Minimal tumor volume (?)
- Patients who express specific molecular markers
 - CA IX (marker for VHL pathway?)
 - Low serum VEGF (marker of tumor volume?)
 - Low serum fibronectin

Targeting Molecular Signaling Pathways in RCC

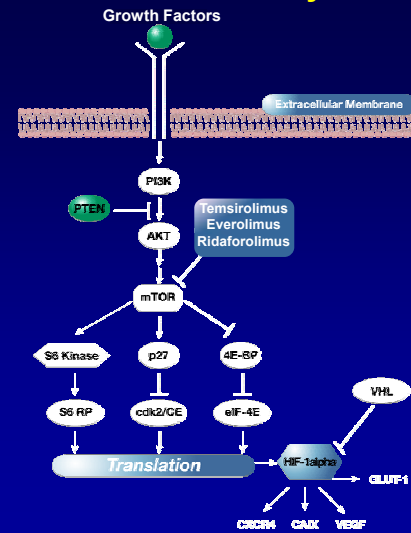
VHL Protein: Normal and Aberrant Function



HIF=hypoxia-inducible factor; hp=hydroxyproline; PDGF=platelet-derived growth factor; VEGF=vascular endothelial growth factor.

Rini. *J Clin Oncol.* 2005;23:1028. Reprinted with permission from the American Society of Clinical Oncology.

mTOR Pathway



Reproduced with permission from Pantuck. *Cancer.* 2007;109:2257.

Clinical Use of Targeted Agents for Patients With RCC

New Standards for Clear-Cell RCC Therapy: Targeted Agents

Agent	PFS	OS	Setting
Sunitinib	11 mo	26.4 mo	First line vs IFN- α
Temsirolimus	5.5 mo	10.9 mo	First line, poor-risk pts. vs IFN- α
Bevacizumab (AVOREN)	10.4 mo	23.3 mo	First line with IFN- α vs placebo with IFN- α
Bevacizumab (CALGB 90206)	8.4 mo	18.3 mo	First line with IFN- α vs IFN- α monotherapy
Sorafenib	5.5 mo	17.8 mo	Second line vs placebo
Everolimus	4.9 mo	NA	Second line vs placebo

NA=not available; OS=overall survival; PFS=progression-free survival.

Motzer. *N Engl J Med.* 2007;356:115; Motzer. *J Clin Oncol.* 2009;22:3584; Hudes. *N Engl J Med.* 2007;356:2271; Escudier. *ASCO.* 2009 (abstr 5020); Rini. *ASCO.* 2009 (abstr LBA5019); Escudier. *N Engl J Med.* 2007;356:124; Escudier. *J Clin Oncol.* 2009;27:3312; Kay. *ASCO GU.* 2009 (abstr 278).

New Standards for Clear-Cell RCC Therapy

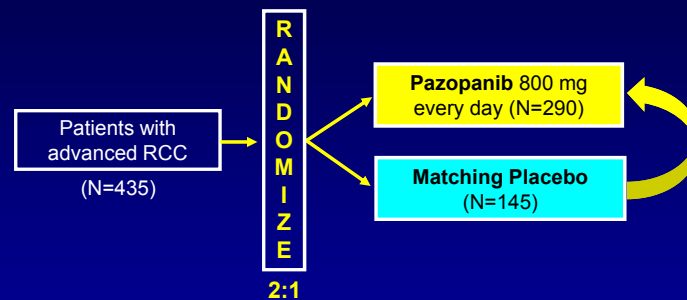
	Setting	Therapy	
First-Line Therapy	Good or intermediate risk*	Sunitinib	High-dose IL-2
		Bevacizumab + IFN- α	
	Poor risk*	Temsirolimus	
Second-Line Therapy	Prior cytokine	Sorafenib	
	Prior VEGFR inhibitor	Everolimus	
	Prior mTOR inhibitor	No data available	

*MSKCC risk status.

MSKCC=Memorial Sloan-Kettering Cancer Center.

National Comprehensive Cancer Network Web site. Kidney Cancer v.1.2010.
http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Accessed 9/23/09.

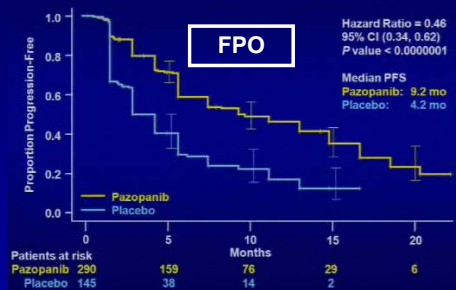
Recent Phase III Trials: Pazopanib vs Placebo in Advanced mRCC



Option to receive pazopanib via an open-label study at progression.

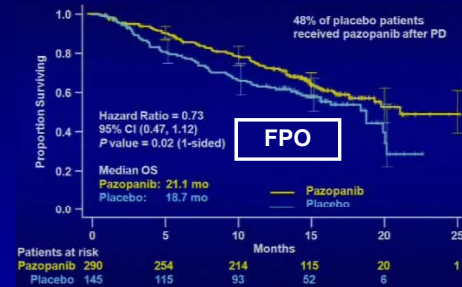
Sternberg. ASCO. 2009 (abstr 5021).

Pazopanib vs Placebo in Advanced mRCC: Interim Analysis PFS



Sternberg. ASCO. 2009 (abstr 5021).

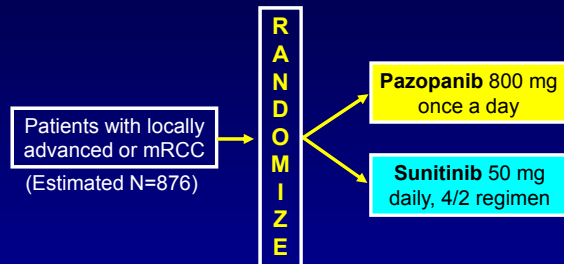
Pazopanib vs Placebo in Advanced mRCC: Interim Analysis OS



- Most common grade 3/4 adverse events with pazopanib: hypertension, asthenia, diarrhea

Sternberg. ASCO. 2009 (abstr 5021).

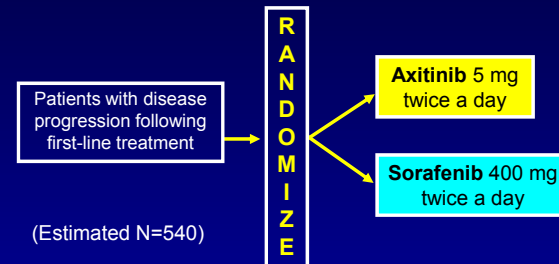
Ongoing Phase III Trials: Pazopanib vs Sunitinib in First-Line mRCC



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, time to response, response duration, safety, and health outcomes analysis

US National Institutes of Health Web site. <http://clinicaltrials.gov/ct2/show/NCT00720941>. Accessed 10/12/09.

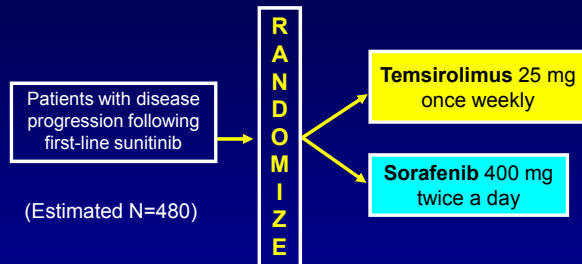
Ongoing Phase III Trials: Axitinib vs Sorafenib in Second-Line mRCC



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, safety and tolerability, and response duration

US National Institutes of Health Web site. <http://clinicaltrials.gov/ct2/show/NCT00678392>. Accessed 10/6/09.

Ongoing Phase III Trials: Temsirolimus vs Sorafenib in Second-Line mRCC



- Primary endpoint: to compare safety, tolerability and efficacy (as measured by PFS)
- Secondary endpoints: PFS, ORR, OS, SD, duration of response, maximum tumor shrinkage in target lesions

SD=stable disease.

US National Institutes of Health Web site. <http://clinicaltrials.gov/ct2/show/NCT00474786>. Accessed 10/12/09.

Recent Updates on Novel Targeted Agents for Patients With mRCC: Phase II

Agent	Target	Setting	ORR
ABT-869	RTKs	Second line, sunitinib refractory	20%
AV-951	RTKs	No prior VEGF-targeted therapy	26%
Cediranib	RTKs	First line	38%
Foretinib (GSK1363089)	MET/VEGFR2	Papillary RCC	11%
Perifosine	AKT/MAPK/JNK	1 prior VEGFR inhibitor and/or 1 prior mTOR inhibitor	3%
Volociximab	$\alpha_5\beta_1$ integrin	TKI- or cytokine-refractory mRCC	2.5%

RTK=receptor tyrosine kinase; TKI=tyrosine kinase inhibitor.

Tannir. ASCO. 2009 (abstr 5036); Bhargava. ASCO GU. 2009 (abstr 283); Sridhar. ASCO. 2008 (abstr 5047); Srinivasan. ASCO. 2009 (abstr 5103); Vogelzang. ASCO GU. 2009 (abstr 302); Yazji. ASCO. 2007 (abstr 5094).

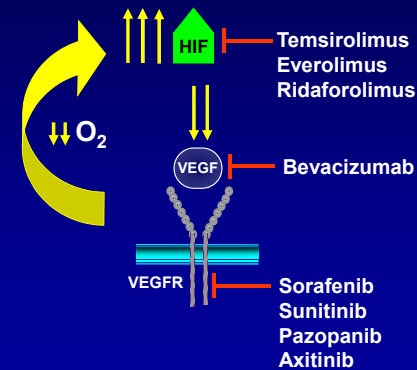
Optimizing Targeted Treatment in mRCC

- Single targeted agents rarely induce CRs
 - Patients develop resistance over time
- Ongoing studies are evaluating specific sequences and combinations of targeted agents
- Combining targeted agents might
 - Increase efficacy
 - Impede onset of refractory disease
 - Overcome resistance to single-agent therapy
 - Increase toxicity/produce novel toxicities

Sosman. *Clin Cancer Res.* 2007;13:764s; Rini. *Clin Cancer Res.* 2007;4:1098.

Combination Therapies: Vertical Blockade of Single Pathways

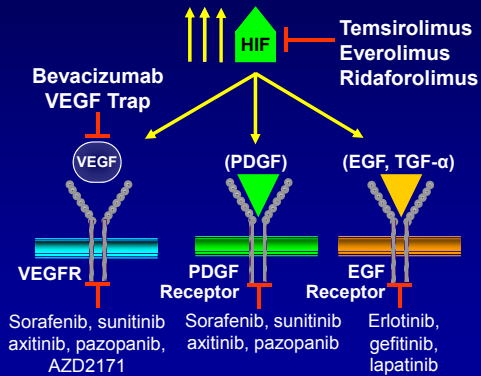
- Vertical blockade
 - Combination of agents that disrupt VEGF pathway at multiple levels



Adapted with permission from Kaelin. *Clin Cancer Res.* 2004;10:6290s; Atkins. ASCO. 2006 Plenary session.

Combination Therapies: Horizontal Blockade of Multiple Pathways

- Combination of agents that inhibit multiple HIF-response growth factors or their receptors



Adapted with permission from Kaelin. *Clin Cancer Res.* 2004;10:6290s; Atkins. ASCO. 2006 Plenary session.

Evolution of Risk Stratification and Clinical Predictors of Response to Targeted Therapies

Hypertension: Prognostic Marker With Sunitinib

- Retrospective analysis of patients treated with first- or second-line sunitinib

	Pts (N=544)	ORR	PFS	OS
Systolic HT (≥ 140 mm Hg)	81%	54.7%	12.5 mo	30.5 mo
No Systolic HT	19%	9.7%	2.5 mo	7.8 mo
Diastolic HT (≥ 90 mm Hg)	67%	57.2%	13.4 mo	32.1 mo
No Diastolic HT	33%	25%	5.3 mo	15 mo

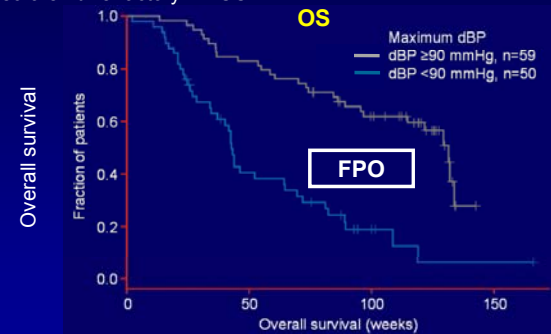
- ORR did not differ significantly between patients who were taking antihypertensive medication at baseline and those who were not

HT=hypertension.

Rini. KCA. 2009.

dBP: Prognostic Marker With Axitinib

- Analysis of pharmacokinetic data from patients with cytokine- or sorafenib-refractory mRCC



- Increased axitinib exposure and dBP ≥ 90 mm Hg were independently associated with longer OS, increased probability of a PR, and greater decreases in tumor size

dBP=diastolic blood pressure.

Rixe. ASCO. 2009 (abstr 5045).

Prognostic and Predictive Molecular Biomarkers in the New Era of Targeted Therapy for mRCC

Prognostic and Predictive Factors for Targeted Therapies

- Molecular analysis of biomarkers allows for assessment of whether a relationship exists between biomarker status and treatment outcome from targeted therapy
- Prognostic and predictive biomarkers might
 - Identify subsets of patients likely to benefit from specific targeted therapies
 - Impact clinical trial design by dissecting treatment efficacy across patient subsets
 - Permit individualized therapy based on the molecular signature of the tumor

Molecular Prognostic Factors Applicable to Cytokine Therapy in RCC

Factor	Expression	Consequence	Other
CA IX	Low	Poor survival	Expression regulated by HIF1- α ; associated with higher T, nodal involvement, and higher grade
Ki67 + CA IX	High Low	High-risk disease	Ki67 is a nuclear antigen and marker for proliferating cells
p21 (localized RCC)	High	Better prognosis	Cell cycle- and apoptosis-regulating protein
p21 (mRCC)	High	Worse prognosis	
p53	High	Higher recurrence rate	Tumor suppressor and cell cycle checkpoint protein

CA=carbonic anhydrase.

Bui. *Clin Cancer Res.* 2003;9:802; Bui. *J Urol.* 2004;171:2461; Atkins. *Clin Cancer Res.* 2005;11:3714; Patard. *Int J Cancer.* 2008;123:395; Weiss. *J Urol.* 2007;177:63; Shvarts. *J Urol.* 2005;173:725.

VHL Status: Predictive of Response to VEGF-Targeted Therapy

- 123 patients analyzed: clear-cell histology, prior nephrectomy (98%), good PS

Overall Response in Relation to VHL Status by Therapy			
Therapy	Mutated	Methylated	Wild Type
	No./Total No.		
Sunitinib	18/32 (56%)	2/6 (33%)	13/25 (52%)
Axitinib	3/8 (38%)	0/1 (0%)	3/5 (60%)
Sorafenib	2/10 (20%)	0/2 (0%)	0/16 (0%)
Bevacizumab	4/9 (44%)	0/3 (0%)	0/5 (0%)

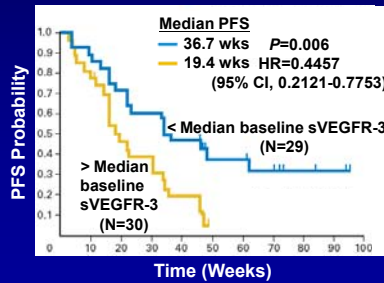
- Patients with a mutated or methylated VHL gene had an ORR of 41% compared with 31% in patients with wild-type VHL ($P=0.34$)
- ORR to VEGF-targeted therapy 52% in patients with loss-of-function VHL mutations vs 31% in patients with wild-type VHL ($P=0.04$)
- PFS and OS not significantly different based on VHL status

Choueiri. *J Urol.* 2008;3:860.

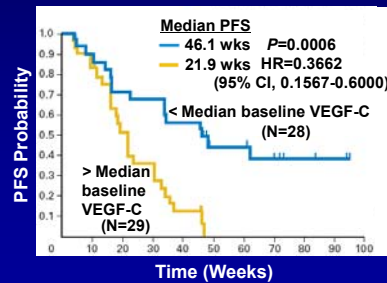
Prognostic Value of sVEGFR-3 and VEGF-C: Sunitinib

- Patients with bevacizumab-refractory mRCC who received sunitinib (N=61)

Correlation of PFS With Baseline Levels of sVEGFR-3



Correlation of PFS With Baseline Levels of VEGF-C

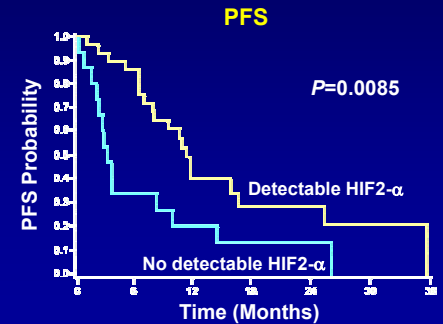


Rini. *J Clin Oncol*. 2008;26:3743.

HIF2- α Predicts Response to Sunitinib

- 43 specimens from patients with clear-cell mRCC treated with sunitinib
- Expression levels of HIF2- α correlated with patient response to sunitinib and PFS

HIF2- α Levels	CR/PR (N)	SD/PD (N)	ORR
None	2	13	15%
Low	4	11	27%
High	12	1	92%



Reproduced with permission from Patel. ASCO. 2008 (abstr 5008).

Prognostic Biomarkers for mTOR Inhibitors in RCC

- 375 specimens from nephrectomized patients with RCC

Factor*	Incidence in Renal Tumors	Consequence
Nuclear pAkt	61%	Favorable prognosis
Cytoplasmic pAkt	93%	Poor prognosis
PTEN	96%	Favorable prognosis
pS6	85%	Poor prognosis

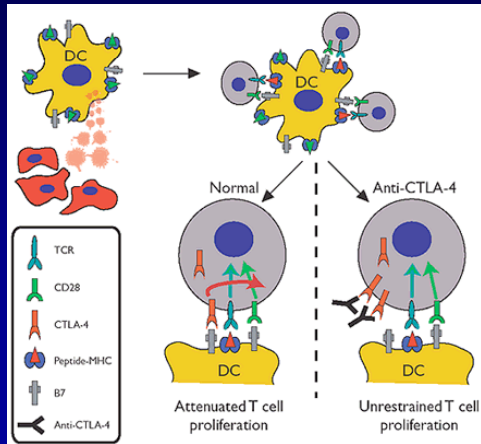
*High expression.

Pantuck. *Cancer*. 2007;109:2257.

Novel immunotherapy approaches

B7 family receptors/antagonists

CTLA-4 MAb



CTLA-4 MAb

- 1) Fully human monoclonal antibody MDX010
- 2) Dosed every 3 weeks i.v.
- 3) Very potent and selective
- 4) There are other lymphocyte inhibitory/costimulatory molecules
 - PD-1, PD-1L and other antagonist MAb in trials
 - CD40 MAb (agonist)
 - Early signs of clinical activity

MDX-010 in melanoma

Induces immune-mediated anti-tumor activity

Objective responses in 10-15%, 1-5% CR

Responses or stable disease durable
(often lasting >12 mo)

May be slow to appear (~ 6 months)

Potential synergy with chemotherapy, vaccines or
immunotherapy agents

Potential to inhibit multiple tumor types

Side effects of MDX-010

- Toxicity:
 - rash, pruritus
 - Autoimmune breakthrough events (ABE):
 - Colitis
 - Vitiligo
 - Endocrine organ failure (hypothyroidism, hypopituitarism)
- Delayed onset
- ABE may correlate with clinical response

MDX-010 in renal cancer

- Phase II study of ipilimumab at Surgery branch NCI
 - Cohort 1: 3 mg/kg followed by 1 mg/kg every 3 weeks
 - Cohort 2: all doses at 3 mg/kg every 3 weeks
- Major toxicities were enteritis and endocrine deficiencies
 - One of 21 Cohort 1 patients had PR.
 - Five of 40 Cohort 2 patients had PR
- Responses were seen in patients who had previously not responded to IL-2.
- Association between ABE and tumor regression?

Yang JC, et al. *J Immunother*. 2007 Nov-Dec;30:825-30.

Summary and Future Directions

- Targeted agents have demonstrated significant single-agent activity in phase III trials for mRCC
 - Survival has increased 3-4 fold in mRCC
 - Attempts to define sequence and decrease toxicity
 - Ongoing studies are assessing targeted agent combinations
- Unanswered questions remain
 - Optimal dosing, sequencing, combinations, and toxicity of targeted agents
 - Evaluating tumor resistance to targeted therapies
 - Validation of prognostic/predictive factors in clinical trials
 - Role of remission-inducing agents

Sosman. *Clin Cancer Res*. 2007;13:764; Chowdhury. *Nat Clin Pract Oncol*. 2008;5:698; Chowdhury. *Eur J Cancer*. 2008;44:2152.