Metastatic Kidney Cancer: Recent Advances and Future Opportunities

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Treatments for RCC Therapy: Summary of Phase III Trial Results

Agent	PFS	OS	Setting
IFN	3 mo	13 mo	First line, meta-analysis
HD IL-2	3 mo	17 mo	First line vs LD IL-2/IFN
Sunitinib	11 mo	26.4 mo	First line vs IFN-α
Pazopanib	11.1 mo	21.1 mo	First- line vs placebo
Bevacizumab (AVOREN/ CALGB 90206)	10.4 mo 8.4 mo	23.3 mo 18.3 mo	First line with IFN-α vs IFN-α
Temsirolimus	5.5 mo	10.9 mo	First line, poor-risk pts. vs IFN-α
Sorafenib	5.5 mo	17.8 mo	Second line vs placebo
Everolimus	4.9 mo	NA	Second line vs placebo

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); Sternberg. *ASCO*. 2009 (abstr 5021).

Targeted Agents: Common Adverse Events

Adverse Event	Bevacizumab	Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus
Fatigue	+	++	+	+	+	+
Rash	-	-	+	-	+	+
Hand-foot syndrome	-	+	++	+	-	-
Hypertension	+	+	+	+	-	-
Diarrhea	-	+	+	+	+	+
Stomatitis	-	+	-	-	+	+
Myelosuppression	-	+	-	-	+	+
Metabolic syndrome	-	-	-	-	+	+
Epistaxis/bleeding	+	-	-	-	-	-
Proteinuria	++	-	-	-	-	-

New Standards for Clear Cell RCC Therapy

Setting		Phase III	Alternative
1st-Line Therapy	Good or intermediate risk*	Sunitinib	HD IL-2
		Bevacizumab + IFNα	
		Pazopanib	
	Poor risk*	Temsirolimus	Sunitinib
2nd-Line Therapy	Prior cytokine	Sorafenib	Sunitinib or Bevacizumab
		Pazopanib	
	Prior VEGFR inhibitor	Everolimus	Clinical Trials
	Prior mTOR inhibitor	Clinical Trials	

*MSKCC risk status.
Atkins. ASCO 2006 Plenary session; Figlin. *Clin Adv Hematol Oncol*. 2007;5:35; Escudier. *Drugs*. 2007;67:1257; Cho. *Clin Cancer Res*. 2007;13:761s; Atkins. *Clin Cancer Res*. 2005;11:3714.

Targeted Therapy:Caveats/Perspective

- **Activity is robust, but there are few, if any, complete responses**
- **Continued treatment appears required to maintain efficacy**
- **Disease resistance usually develops within 6-12 months for VEGF inhibitors; < 6 mos mTor inhibitors**
- **Survival benefit for VEGF pathway inhibitors has not been firmly established and for temsirolimus is established only in a subset of patients with the most aggressive tumors (benefit = 3.5 mos)**
- **Benefit for everolimus established only against placebo, not against an active treatment**

RCC: Current Opportunities

- **Selection for immunotherapy**
- **New VEGF Pathway Agents**
- **Dose Intensification-based on biomarkers**
- **Sequencing of Agents**
- **Combination Therapy**
- **Novel Treatments/Immunotherapy**

Activity of IL-2 is greater than package Insert

Response*	%
Historical rate	14
IL-2 Select Trial (all pts n=120)*	28

p=0.0016
95% CI=20.5-37.3%

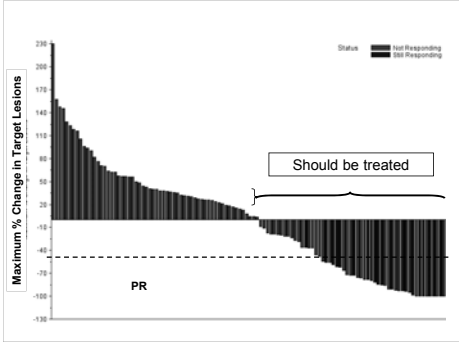
Likely explanations for improved RR include:

1) **Enhanced "pre-screening"**
   - **smaller non-clear cell population**
2) **Impact of alternative therapies on IL-2 referral patterns**
3) **Application of debulking nephrectomy**
   - **fewer patients treated with primary in place**

*Using WHO Criteria

McDermott et al ASCO 2010

Tumor Shrinkage Plot (n=118)



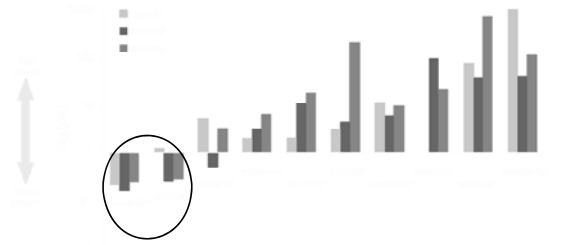
Response by Baseline Characteristics

	RR (95% CI)	P-value*
All Patients (n=120)	28% (20%-37%)	0.0016
Tumor type		
Clear Cell (n=115)	**30% (21%-39%)**	**0.31**
Non-clear cell (n=5)	**0% (0%-52%)**	
MSKCC Risk Group		
Favorable (n=31)	**32% (17%-51%)**	**0.08**
Intermediate (n=83)	**24% (15%-35%)**	
Poor (n=6)	**67% (22%-96%)**	
UCLA Risk Group		
Low (n=10)	**30% (7%-65%)**	**0.22**
Intermediate (n=101)	**30% (21%-40%)**	
High (n=8)	**0% (0%-37%)**	

RCC IL-2 Select Trial: Biomarker Studies

- **CA-9 expression did not predict for response**
- **Efforts to confirm other proposed biomarkers are ongoing**
  - **e.g. CA-9 SNPs, B7H1, B7H3, serum VEGF, gene expression patterns (immune infiltrate)**
- **Given the high RR and comprehensive tissue collection in this trial, an improved model for IL-2 patient selection will likely emerge**
- **Lessons from this work may guide the development of novel immunotherapies (e.g. CTLA-4, anti-PD-1) in mRCC**

More Potent VEGFR TKIs in RCC

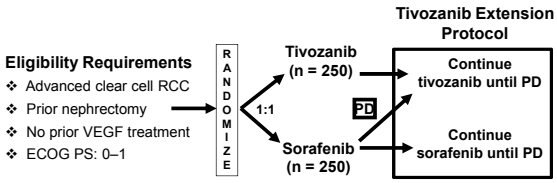


IC_{50} = half-maximal inhibitory concentration.
Eskens et al, 2008; Nakamura et al, 2006; Chow et al, 2007.

VEGF-R Inhibitors in <u>VEGF-targeted Therapy-Naïve</u> RCC Patients

Treatment	Objective Response	% Pts with Tumor Burden Reduction	PFS
Sunitinib	**30 - 45%**	**~ 70-75%**	**11 months (treatment-naïve) 8.4 months (cytokine-refractory)**
Sorafenib	**2% - 10%**	**~ 70-75%**	**5.5 - 5.7 months**
Pazopanib	**30%**	**~ 70-75%**	**9.2 months**
Axitinib	**47%**	**~ 70-75%**	**15.7 months (cytokine-refractory)**
Tivozanib	**24%**	**83%**	**8.9 – 11.8 months 15 mos for ccRCC**

TIVO-1 Trial: Phase III Head-to-Head Trial of Tivozanib Vs. Sorafenib



❖ First head-to-head RCC registration trial vs. an active comparator
- Primary end point: PFS
- Secondary end points: OS, ORR, QOL

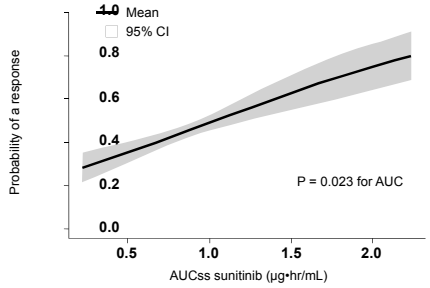
❖ Treatment schedule (1 cycle = 4 wks)
- Tivozanib: 1.5 mg/day for 3 wks, followed by 1-wk break
- Sorafenib: 800 mg/day for 4 wks

QOL = quality of life.
US NIH, 2011a, 2011b.

VEGF Pathway Inhibitors: Commentary

- **Drugs identified as inhibitors of VEGF-R have a diverse spectrum of biochemical, clinical and toxic effects**
  - **Potency appears to correlate with inhibition of VEGFRs**
  - **Unique toxicities relate to non-VEGF pathway targets**
- **Although there is room for improvement on existing therapies, we may be rapidly approaching the limits of inhibition of the VEGF pathway**

Exposure-response of Sunitinib in mRCCC: A PK/PD Approach

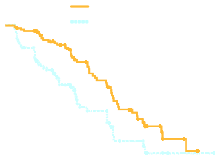


PR = partial response; CD = complete response

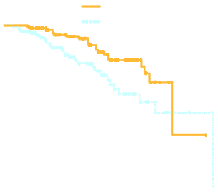
Houk et al, ASCO 2007, Abstract #5027

Longer TTP and OS in mRCC Patients with the Highest Sunitinib Exposure

Time to tumor progression



Overall survival



Houk et al, ASCO 2007, Abstract #5027

Exposure-Response-Sunitinib: Conclusions- Houk et al

- **Maintaining sunitinib dosing may be important**
- **It may ultimately be important to dose patients based on blood levels similar to antibiotics or anti-convulsants**

Hypertension May Predict Prolonged Survival With Sunitinib

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

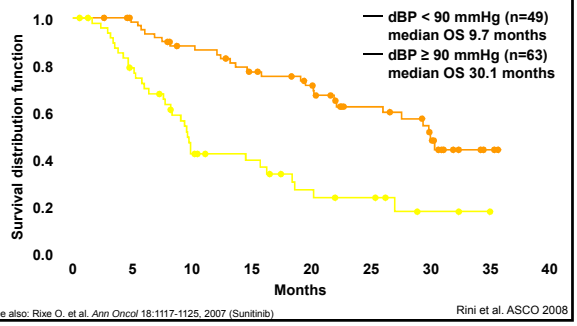
	Pts (N=544)	ORR	PFS	OS
Systolic HT (≥ 140 mm Hg)	81%	54.7 %	12.5 mo	30.5 mo
No Systolic HT	19%	9.7%	2.5 mo	7.8 mo
Diastolic HT (≥ 90 mm Hg)	67%	57.2 %	13.4 mo	32.1 mo
No Diastolic HT	33%	25%	5.3 mo	15 mo

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

HT=hypertension.

Rini. *KCA*. 2009.

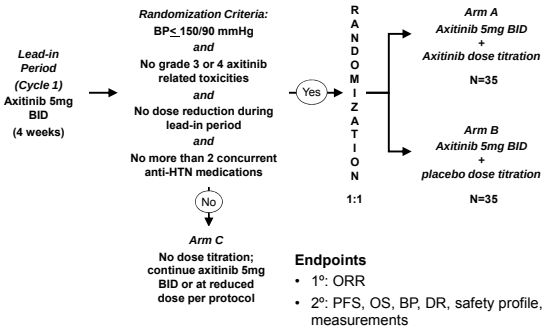
Axitinib: OS in patients with or without dBP ≥ 90 mmHg – pooled mRCC studies



See also: Rixe O. et al. *Ann Oncol* 18:1117-1125, 2007 (Sunitinib)

Rini et al. ASCO 2008

Axitinib prospective dose escalation study



Endpoints

- 1º: ORR
- 2º: PFS, OS, BP, DR, safety profile, measurements

At: http://www.clinicaltrials.gov. ID#NCT00835978. Accessed Oct 28, 2010.

Sequencing of Agents

IL-2 Therapy in Patients with Prior Antiangiogenic Therapy:Retrospective analysis

Patients who did not receive week 2 doses*	**6/23 (26)**
Prior sorafenib or sunitinib	**6/15 (40)**
Prior bevacizumab	**0/8 (0)**

Toxicities that prevented further treatment included:: cardiomyopathy, myocarditis, atrial fibrillation with hypotension and bowel ischemia, severe angina, sudden cardiac arrest, and bullous pemphigoid

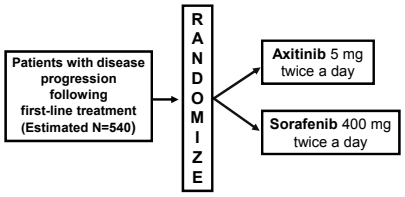
No tumor responses

Cho et al. J Immunotherapy 2009

Results in VEGF-targeted Therapy-refractory RCC Patients

Agent	Population	N	OR / TS	PFS
Sunitinib (Rini et al. *JCO*, 2008)	Phase II: Bev.-refractory	62	23% / 75%	7.1 months
Axitinib (Rini et al. *JCO*, in press)	Phase II: Sorafenib-refractory	62	23% / 55%	7.4 months
Sorafenib (Sheppard et al. ASCO 2008)	Phase II: Bevacizumab or sunitinib-refractory	49	3% / 38%	3.8 months
Everolimus (Motzer et al. Lancet, 2008)	Phase III: TKI-refractory (vs. placebo)	410	2% / 60%	4.9 months (vs. 1.9 months)
ABT-869 (Tannir et al. ASCO 2009)	Phase II: sunitinib-refractory	53	9% / 58%	5.4 months
Perifosine (Vogelzang et al. ASCO 2009)	Phase II: TKI-refractory (+/- mTOR-refractory)	50	11% (13% / 6%)	~ 3 - 4 months

Phase III Trial: Axitinib vs Sorafenib in the Second-Line Treatment of Patients With 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.

Best Response by RECIST
(IRC Assessment)

Best Overall Response, %	Axitinib	Sorafenib
Partial response*	19.4	9.4
Stable disease	49.9	54.4
Progressive disease	21.6	21.0
Indeterminate	6.1	11.6
Risk ratio (95% CI)	2.1 (1.4–3.0)	

*Axitinib vs. Sorafenib: P = 0.0001

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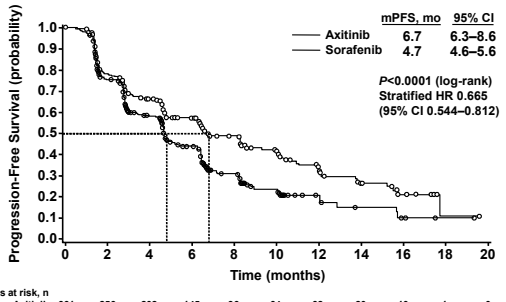
Progression-free Survival
(IRC Assessment)



Subjects at risk, n

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

IRC = Independent Review Committee

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AXIS Trial: PFS by Prior Regimen

Prior Treatment Regimen	Axitinib (n=361)	Sorafenib (n=362)	HR	P value*
Cytokines (n=251)				
IRC	12.1	6.5	0.464	<0.0001
Investigator	12.0	8.3	0.636	0.005
Sunitinib (n=389)				
IRC	4.8	3.4	0.741	0.011
Investigator	6.5	4.5	0.636	0.0002

*One-sided log-rank test stratified by ECOG PS

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Hazard Ratios for PFS by Prognostic Factors and Baseline Characteristics

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Adverse Events*

Event	Axitinib (%)		Sorafenib (%)	
	All grade	Grade 3/4	All grade	Grade 3/4
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Nausea	32	3	22	1
Vomiting	24	3	17	1
Hypothyroidism	19	<1	8	0
Stomatitis	15	1	12	<1
Hand-foot syndrome	27	5	51	16
Rash	13	<1	32	4
Alopecia	4	0	32	0

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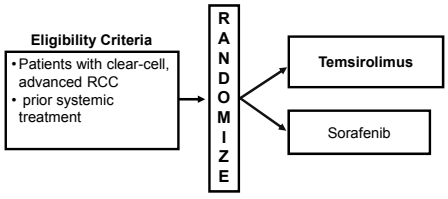
*All-causality; highest AEs of interest

Phase III Trial of Temsirolimus vs Sorafenib in Sunitinib Failures



- Primary endpoints: PFS, safety & tolerability
- Secondary endpoints: ORR, OS, DR

US National Institutes of Health website. http://clinicaltrials.gov/, ID#NCT00474786 Accessed Oct 28, 2010

Sequential Therapy: Summary (1)

- Sequential therapy has become the *de facto* standard in RCC
- Preliminary data suggests that IL-2-based immunotherapy best offered first if at all
- Data suggests activity of VEGF/mTor inhibitor therapy are similar after immunotherapy as in Rx naïve patients
- Axis trial confirms that sequential VEGF pathway inhibition is safe and has antitumor activity
  - Axitinib is superior to sorafenib following either sunitinib or cytokines
  - Ddata support the hypothesis that more potent biochemical targeting of the VEGF receptor is associated with superior clinical activity

Sequential Therapy: Summary (2)

- Phase III data suggest that mTor inhibition is better than placebo in VEGFR TKI resistance
  - Benefit relative to VEGF pathway blocker uncertain
  - Role of maintaining VEGF pathway blockade yet to be explored
- Additional prospective studies and efforts to rationally select second line treatment based on understanding mechanisms of resistance are necessary

Combination Therapy: Issues

- Hitting more targets is not necessarily better
  - Lowering dose of an active agent in order to accommodate toxicity of less active agent might diminish effects
  - Inhibition of some pathways might produce countervailing effects or just additional side effects
- Combination therapy should be based on
  - Knowledge of pathways
  - Understanding mechanisms of resistance/escape
  - Relevant animal models
  - Moved early into “benchmarked” studies

Combination Therapy Trials

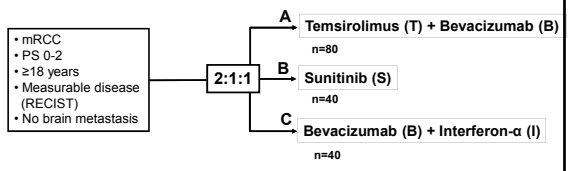
Vertical Blockade

- **Sorafenib + bev- Sosman et al**
  - **52% RR, DLTs required drastic dose reductions**
- **Sunitinib + bev – Feldman et al**
  - **> 50% RR at highest dose, MAHA syndrome with continued dosing**

Horizontal Blockade

- **Bev + erlotinib-Bukowski et al**
  - **No advantage over bev alone**
- **Temsirolimus + Bev- Merchan et al**
  - **Tolerable at full dose, > 50% RR, 12 pts**
- **Everolimus + Bev- Whorf et al**
  - **Tolerable at full dose, active in first and second line**

TORAVA Study Design

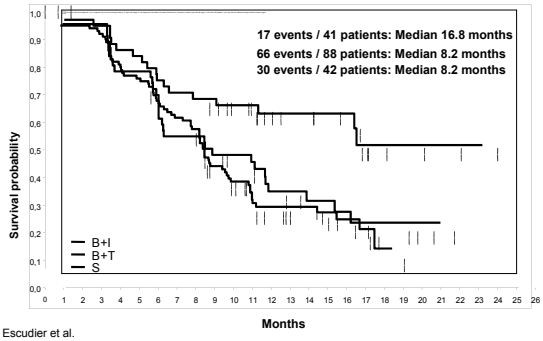


Primary endpoint: Non-progression rate at 48 weeks

T: intravenously 25 mg/week
B: intravenously 10 mg/kg every 2 weeks
S: orally 50 mg/day - 4 weeks-2 off
I: subcutaneously 9 MU*3/week

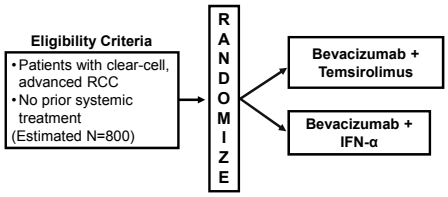
Escudier et al.

TORAVA: PFS



Escudier et al.

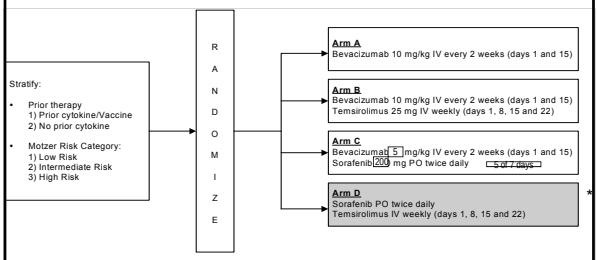
Combination Therapy in RCC: INTORACT Trial



- Primary endpoints: tumor measurements and survival status
- Secondary endpoints: safety, PFS, ORR, and OS

US National Institutes of Health website. http://clinicaltrials.gov/ct2/show/NCT00631371. Accessed 10/6/09.

E2804: BeST Trial- Flaherty and McDermott



1 cycle = 28 days
Accrual goal = 360 patients

* Arm to be added when phase II doses are available from ongoing phase I trials
NOTE: All patients enrolled into the ECOG E2804 study are eligible for participation in the DCE-MRI component of the trial.

Targeted Therapy + Immunotherapy

- **Temsirolimus + IFN**
  - **Less active and more toxic than temsirolimus alone**
- **Bevacizumab + IFN**
  - **Two randomized phase 3 trials prove superior PFS with conflicting OS results**
  - **Additive but not synergistic toxicity**
  - **Confirmed in current trial by Escudier et al.**
- **Sunitinib + IFN: excessive toxicity**
- **Bevacizumab + high-dose IL2**

IL-2 + Bevacizumab – Best Response

	Response	N (%)
?IL-2	Complete Response	4 (8)
	Partial Response	10 (20)
?Bev	Stable Disease	21 (43)
	Progressive Disease	13 (27)
	Withdrawn	1 (2)

Dandamudi, CWG, ASCO 2010.

Combination Therapy: Comment

Combination therapy is more complicated than we had hoped

Vertical Blockade

- **More toxic, requires lower doses**
- **However, may just need to beat best single agent for that pathway**

- **Horizontal Blockade**
  - **More tolerable**
  - **However, bar is higher. Likely needs to be significantly better than sequential therapy**
- **Immunotherapy + Targeted Therapy**
  - **Additive benefit with bevacizumab**
  - **More toxicity with targeted therapies**

Novel Targets

- **Hif 2 alpha**
- **PI3K/Torc 2**
- **PD1**

HIFα Family Members

HIF1α **HIF2α** **HIF3α**

Renal Cell Carcinoma

HIF2α is a critical target in
VHL -/- RCC oncogenesis

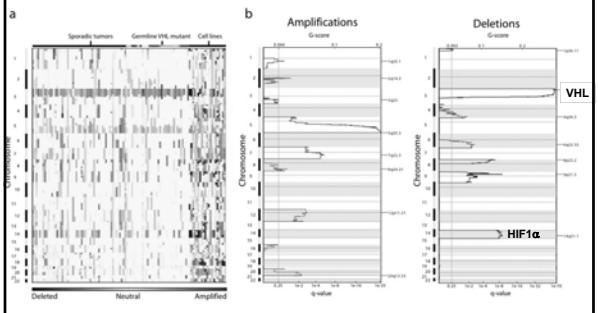
HIF1α Behaves Like a Tumor Suppressor

HIF1α
HIF2α RCC → Decreased Proliferation

HIF1α shRNA
HIF1α +2α RCC → Increased Proliferation

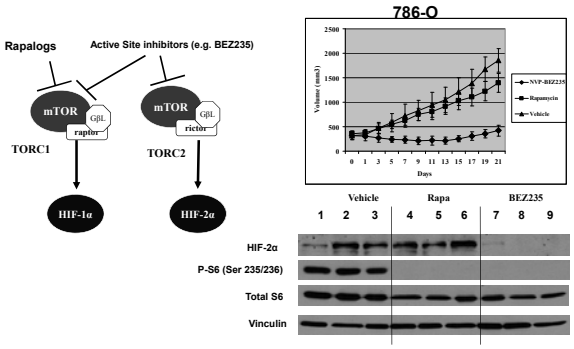
Shen C, Kaelin WG, et al, Cancer Discovery (in press)

Kidney Cancer Copy Number Changes



Beroukhim et al Cancer Research 09

Inhibiting TORC2 and HIF2 in RCC

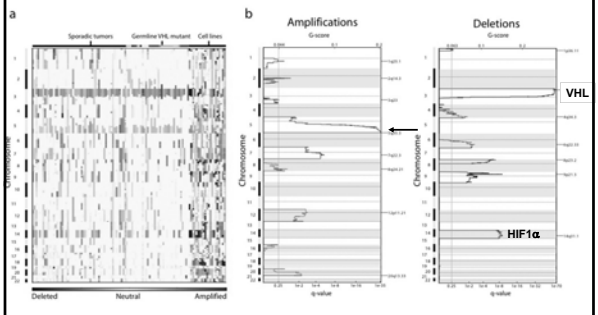


Cho DC. Clin Ca Res 2010; 16(14):3628.

Dual TORC1/TORC2 Pathway Inhibition: Investigator-Initiated Clinical Trials

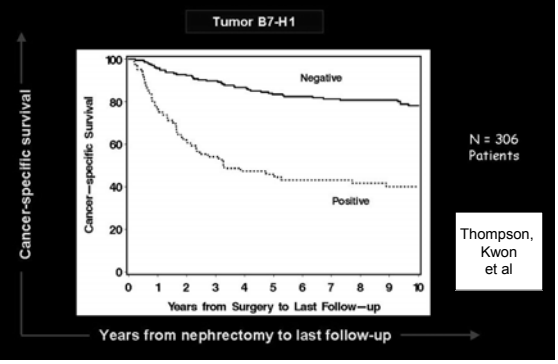
- **Phase II Biomarker Trial of BEZ235 in patients with RCC (Cho)**
- **E2811: Cooperative Group Randomized phase II Trial of OSI-027 vs everolimus in patients with VEGFR TKI resistant RCC- (Cho)**

Kidney Cancer Copy Number Changes



Beroukhim et al Cancer Research 09

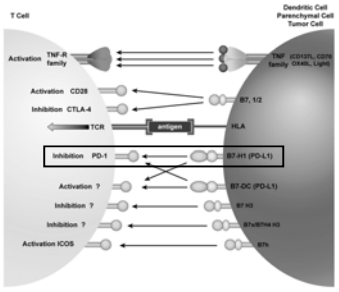
Increased B7-H1 Expression in RCC Diminishes Survival



N = 306 Patients

Thompson, Kwon et al

Enhancing Immune Responsiveness

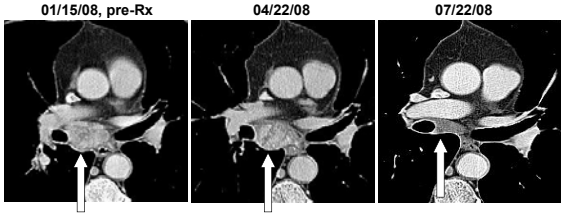


PD1 Ab (MDX1106) Phase I, single dose, Tolerable, responses in Colon, Lung, MM, RCC Brahmer, ASCO 2008

PDL1 Ab Phase I trial ongoing

PD1 Ab Phase 1, multi dose, tolerable, PRs in RCC, MM and Lung, Sznol, ASCO 2010

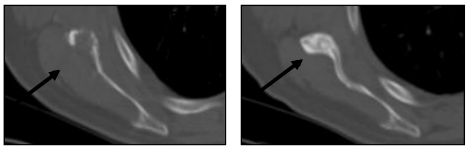
Durable partial regression of metastatic kidney cancer following 3 doses of anti-PD-1 (10 mg/kg)

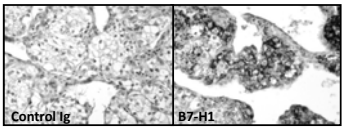


72 year old male with RCC metastatic to lung, LN, muscle, bone, pancreas. Prior therapies included HDAC inhibitor, sunitinib, and sorafenib.

Brahmer et al., JCO 2010

Resolving RCC lytic bone metastasis in patient treated with anti-PD-1 (10 mg/kg)





Responses may be correlated with PD-L1 expression
3/4 PRs in PDL-1+ tumors, 0/5 PDL-1 neg

Brahmer et al., JCO 2010

Updated Clinical Activity in RCC Patients

*

Response	RCC Patients (n = 16)
PR, n (%)	5 (31.3)
uPR, n (%)	1 (6.3)
SD ≥6 months, n (%)	7 (43.8)

*Patients treated with the 10 mg/kg dose
Abbreviations: PR = partial response; RCC = renal cell carcinoma; SD = stable disease; uPR = unconfirmed partial response

McDermott et al GU ASCO 2011

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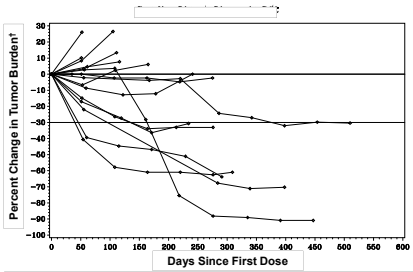
Percent Change in Tumor Burden in RCC Patients



*Patients treated with the 10 mg/kg dose
†Upper horizontal line denotes no change; lower horizontal line denotes 30% decrease (RECIST threshold for PR).

Abbreviations: PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors

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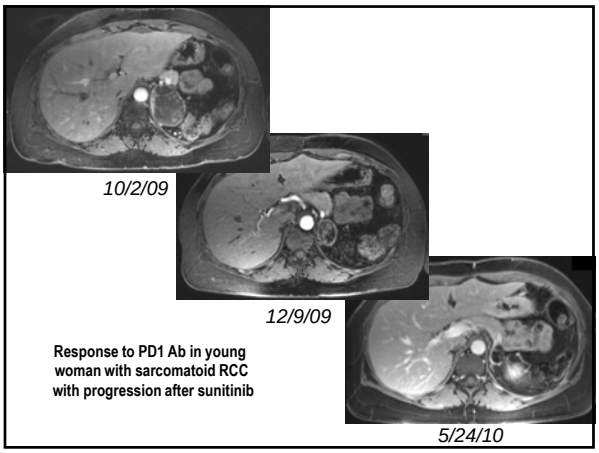

Response to PD1 Ab in young woman with sarcomatoid RCC with progression after sunitinib

PD-1 Ab Summary

- **Acceptable tolerability at all dose levels tested**
  - **-MTD not reached at 10 mg/kg**
- **Adverse event profile consistent with an immunomodulatory mechanism of action**
- **Anti-tumor activity observed in patients with RCC, melanoma and NSCLC**
  - **-Responses appear durable**
- **Phase 2 dose and schedule still under evaluation**
- **Opportunity for targeted immunotherapy with possible biomarker selection**

Trials To Watch: 2011 and Beyond

Regimen	Group	Status
Pazopanib vs Sunitinib	GSK	Results soon
Tivozanib vs Sorafenib	Aveo	ASCO 2012
E2804 - 4 arm combination (BeST)	ECOG	ASCO 2012
Tor inhibitor + Bev first line trials (TORAVA, INTORACT)	France Industry	ASCO 2010, Near completion
RECORD-3: Sunitinib to everoliums vs everolimus to sunitinib	Pfizer	Accruing
RAD+/- Bev in VEGFR TKI failures	CALGB	Accruing
Tems vs Sorafenib in TKI failures	Wyeth	Nearing completion
Phase II Anti-PD1 Ab trial	BMS	Nearing activation

Future Challenges/Opportunities

- Biomarker studies
  - Imaging
  - Blood-based
  - Early detection
- Mechanisms of resistance
- Adjuvant Therapy
- Role of cytoreductive Nx and neoadjuvant Rx
- Therapy for non-clear cell RCC