

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

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Summary

The treatment of renal cancers is evolving very quickly. As knowledge of the molecular pathways key to the growth of cancer cells has become available, targeted therapies that disrupt these pathways have been developed. Although many questions remain about the optimal use of these agents, the median survival time for patients has been significantly increased.

Key Points

- There are several subtypes of kidney cancer histology which predict response to treatment and prognosis.
- The most common subtype, clear cell, involves von Hippel-Lindau mutations.
- The discovery of important metabolic pathways for growth and survival of renal cancers lead to targeted treatments which disrupt these pathways and lead to cancer cell death.
- With the use of targeted treatments, median survival for metastatic RCC has increased significantly from 10 - 13 months to 4 years.

CANCERS OF THE KIDNEY ARE RELATIVELY uncommon accounting for 5 percent of all cancers in men and 2.5 percent in women.¹ In 2009, an estimated 57,760 cases of renal cell carcinoma (RCC) were diagnosed.¹ An alarming trend is that the incidence is increasing 2.5 percent per year. There is a question whether this increase is real or due to better diagnosis.²

Unfortunately, RCC is often diagnosed in the advanced stages so prognosis in the typical patient is not good. Five years ago, the median survival for metastatic RCC (mRCC) was 10 to 13 months. Approximately 13,000 deaths from RCC occur each year.¹

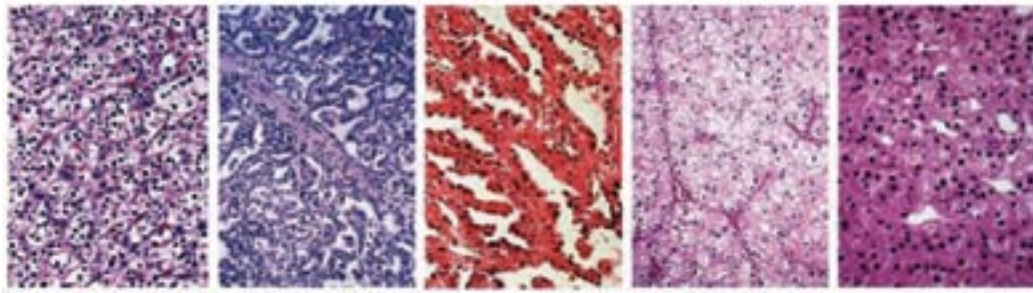
In years past, kidney cancer was always just diagnosed as renal cell carcinoma. It is now understood that there are several subtypes of histology which predict response to treatment and prognosis (Exhibit 1).³ In the rare patient who has a family history of renal cancer, the genes associated with each type of histology have been identified. Identification of von Hippel-Lindau (VHL) mutations being present in 75 percent of renal cancers lead to development of

treatments that target this mutation.

In 1980, there were no effective treatments for mRCC. Patients were treated with chemotherapy and hormonal therapy with very little response. Beginning in 1987, immunotherapy agents, interferon-alpha and interleukin 2, that activated the immune system against cancer came into use. These agents provided a benefit in a minority of patients. With interferon, five to seven percent of patients had complete responses and have remained free of disease. Unfortunately, the costs and adverse effects of immunotherapy were significant. Additionally, interferon requires chronic use. Because it was easy to give, it became the community standard of care for mRCC. Even now, there is not a clear test to identify the patients who will respond to interferon.

Interleukin 2, which activates T cells to kill cancer cells, causes a release of inflammatory cytokines. The resulting cytokine storm leads to the many significant adverse effects of this agent. This agent requires intravenous infusions in a specialized treatment center. Interleukin 2 can significantly reduce the size of renal tumors (Exhibit 2). Ten to 15 per-

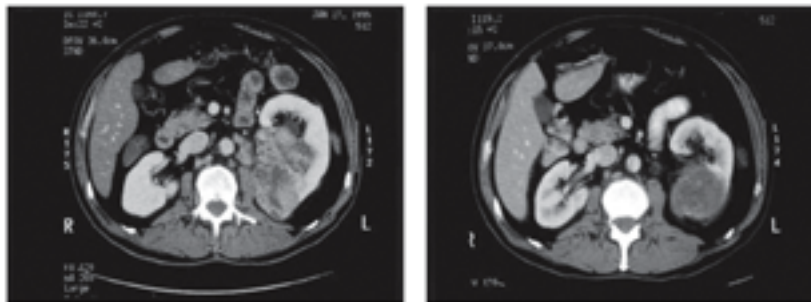
Exhibit 1: Histologic Subtypes³



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

Exhibit 2: Why use IL-2?



A

B

cent of patients have dramatic improvement and long term survival. The patients who benefit from interleukin 2 have a high performance status, the clear cell histology, minimal tumor volume, and express specific molecular markers.

The biggest advance in mRCC treatment has come with targeted therapy against the molecular pathways for tumor growth that have been identified. In 2004, targeted therapy with signaling inhibitors became available. The first two types of signaling inhibitors are vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors. With targeted therapy, the median survival has increased to four years. The price tag for this increased survival is \$300,000 to \$500,000.

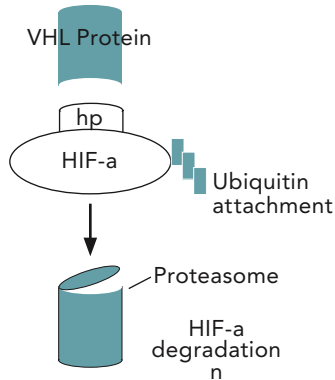
The first of the molecular pathways in RCC cells that was identified was VHL. Under normal condi-

tions and in the presence of oxygen, VHL protein mediates the degradation of transcription factors that regulate gene expression. If the tumor has a mutation in this protein or there is hypoxia, the VHL protein does not function allowing transcription factors to bind to DNA (Exhibit 3).⁴ This leads to the production of specific proteins – VEGF and platelet derived growth factor (PDGF). These proteins are involved in the growth of blood vessels which is important in highly vascular tumors such as RCC. The identification of the importance of VEGF and PDGF lead to the development of therapies specifically targeted against them.

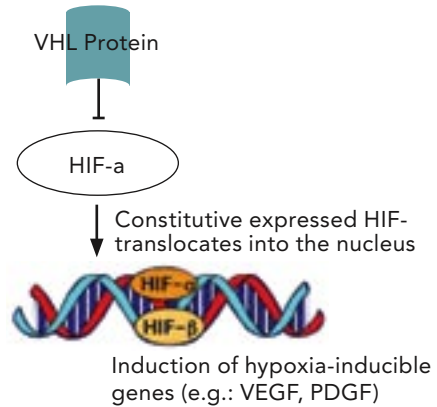
Another identified pathway is mTOR (Exhibit 4).⁵ Cell growth factors are linked through a series of signaling steps with a kinase (mTOR) which leads downstream to metabolic activity in cells. The intermediate steps in this pathway can be targeted

Exhibit 3: Normal and Aberrant Function VHL Protein⁴

Normoxia and Normal VHL Protein Function



Hypoxia or Abnormal VHL Protein Function



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

with medications to disrupt the pathway.

Exhibit 5 shows the currently approved targeted therapies for clear cell RCC.⁶⁻¹⁰ Sorafenib was the first targeted agent approved by the FDA. It was approved for second line therapy in patients who failed interleukin 2 or interferon. This agent doubled the

progression free survival compared with placebo. Sunitinib, the second agent approved, leads to a longer progression free survival and overall survival rates of 2 years.

The current National Comprehensive Cancer Network recommendations for selecting which of

Exhibit 4: mTOR Pathway⁵

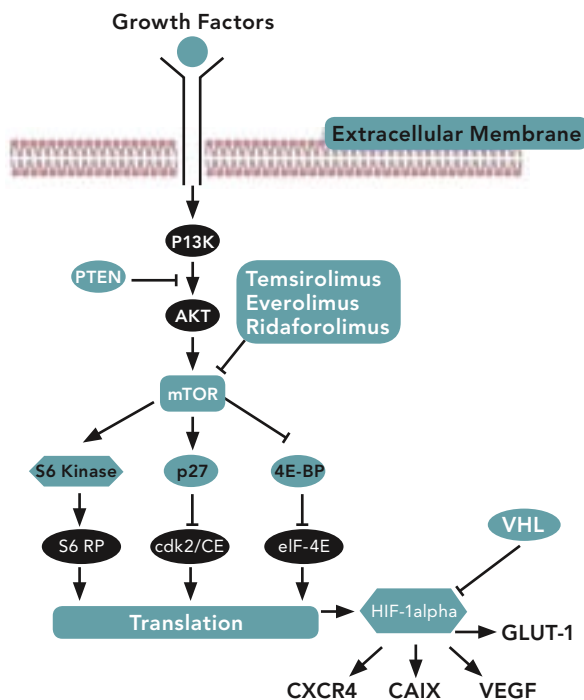


Exhibit 5: Targeted Agents for Clear-Cell RCC Therapy⁶

Agent	PFS	OS	Clinical Trial Setting
Sunitinib	11 mo.	26.4 mo.	First line vs IFN-
Temsirolimus	5.5 mo.	10.9 mo.	First line, poor-risk pts. vs IFN-
Bevacizumab	10.4 mo.	23.2 mo.	First line with IFN- vs placebo with IFN-
Bevacizumab	8.4 mo.	18.3 mo.	First line with IFN- vs IFN- 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.

Exhibit 6: New Standards for Clear-Cell RCC Therapy¹¹

	Setting	Therapy
First-Line Therapy	Good or intermediate risk*	Sunitinib Bevacizumab + IFN- Pazopanib High-dose IL-2
	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)

these agents to use is detailed in Exhibit 6.¹¹ With these new agents which have relatively low rates of adverse effects, patients can maintain a near normal quality of life with an increased life span compared with the older agents and no treatment.

Studies are ongoing to further refine the roles for each of the targeted agents and to evaluate additional agents. One study is comparing pazopanib, which may be better tolerated than earlier agents, with sunitinib. Another trial is comparing axitinib, an agent approved for metastatic thyroid cancer and active in kidney cancer, with sorafenib as second line treatment in mRCC.

Single targeted agents rarely induce complete responses. The tumors 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, and overcome resistance to single-agent therapy. The downside is that combinations may increase toxicity or result in novel toxicities.

Vertical and horizontal blockade are two ideas that has been tested. Vertical blockade involves blocking multiple steps in a single signaling pathway (Exhibit 7). A problem seen with a vertical blockade with multiple agents that affect VEGF is marked hypertension in 100 percent of patients and new adverse effects that are not seen with each agent individually. Horizontal blockade blocks several different pathways (Exhibit 8).

Risk stratification using clinical predictors of re-

Exhibit 7: Combination Therapies: Vertical Blockade of Single Pathways

Combination of agents that disrupt VEGF pathway at multiple levels

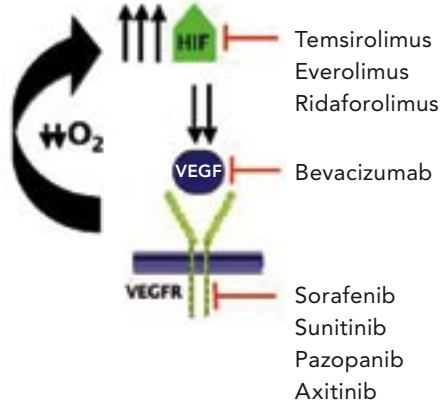


Exhibit 8: Horizontal Blockade of Multiple Pathways

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

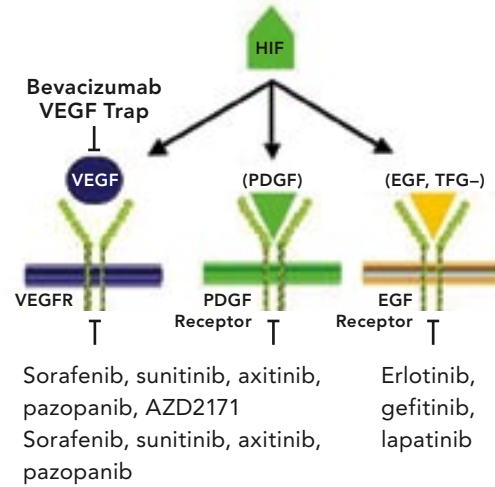


Exhibit 9: Molecular Prognostic Factors Applicable to Cytokine Therapy in RCC¹²⁻¹⁷

Factor	Expression	Consequence	Other
CAIX	Low	Poor survival	Expression regulated by HIF1-; associated with higher T, nodal involvement, and higher grade
Ki67 + CAIX	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.

sponse to targeted therapies is evolving. There is a lot of work going on to identify which patients will respond to which agents. Molecular analysis of biomarkers allows for assessment of whether a relationship exists between biomarker status and treatment outcome from targeted therapy. Prognostic and predictive markers are being identified. Prognostic markers are identified at the onset that determine how people are going to do and predictive ones suggest whether a particular therapy will be effective. Prognostic and predictive biomarkers might iden-

tify subsets of patients likely to benefit from specific targeted therapies, impact clinical trial design by dissecting treatment efficacy across patient subsets, and permit individualized therapy based on the molecular signature of the tumor.

Examples of prognostic biomarkers are shown in Exhibit 9.¹²⁻¹⁷ For example, low carbonic anhydrase nine expression predicts poor survival.

One example of a predictive marker of response is hypertension with sunitinib or axitinib. Patients who develop increases in blood pressure while on

these agents have a much higher response rate.¹⁸ VEGF signals a compound that dilates blood vessels. Blocking VEGF prevents this dilation resulting in hypertension. It may be that the more effectively VEGF is blocked, the better the agent works.

Another predictive marker for response to any agent studied so far in clear cell RCC is VHL status. Patients with a mutated or methylated VHL gene have a higher overall response rate to therapy compared with patients with wild-type VHL.¹⁹

There are many unanswered questions about targeted therapies. Optimal dosing, sequencing, combinations, and toxicity of targeted agents has not yet been defined. Additionally, issues of tumor resistance to targeted therapies must be resolved. Validation of prognostic and predictive factors in clinical trials is needed.

The future holds more promise for managing RCC. Agents targeting other pathways such as kinases and integrin are under study. There are several novel immunotherapy approaches on the horizon for the treatment of mRCC. One of these, ipilimumab, is a monoclonal antibody that increases the likelihood of T cell activation so the cell can kill cancer cells. This is a fully human monoclonal antibody that is given every three weeks by intravenous infusion. This antibody appears to be effective in many different cancers including RCC and may eventually be used in combination with targeted therapies or chemotherapy.

Conclusion

Targeted agents have demonstrated significant single-agent activity in clinical trials for mRCC. Survival has increased 3 to 4 fold in mRCC. There are ongoing attempts to define the optimal sequence and combination of these agents. Many unanswered questions remain but it is an exciting era for the treatment of mRCC. JMCM

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