



Newsletter of the DF/HCC Kidney Cancer Program

www.dfhcc.harvard.edu/renalcancer

Winter 2009

In this issue:

- 2** HIF2α: Critical Factor in RCC is Target of Novel Drug Delivery Strategy
- 2** Analgesics implicated in Kidney Cancer Risk and Prevention
- 3** Angiopoietins: Alternative Angiogenic Pathway to be Inhibited in DF/HCC-led, Combination Anti-angiogenic Therapy Trial
- 3** In the News / Awards
- 4** Current Clinical Trials



Beth Israel Deaconess Medical Center



DANA-FARBER CANCER INSTITUTE



BRIGHAM AND WOMEN'S HOSPITAL



MASSACHUSETTS GENERAL HOSPITAL



Children's Hospital Boston



Harvard Medical School



Harvard School of Public Health

From the Program Director

By Michael B. Atkins, MD, Beth Israel Deaconess Medical Center, Leader, DF/HCC Kidney Cancer Program

The past three years have witnessed a virtual revolution in the treatment of patients with advanced renal cancer. Clinical investigations have documented activity for drugs that target vascular endothelial growth factor (VEGF) driven tumor angiogenesis and the mTOR pathway, resulting in the FDA approval or pending approval of 5 novel agents and an improvement in median overall survival from 13 months with IFN alpha therapy to in excess of 27 months with sequentially administered treatments. Taken together, the recent phase III investigations have led to the creation of an "evidence-based" algorithm for treatment selection with sunitinib or bevacizumab plus IFN alpha being favored for front-line therapy in patients with good or intermediate prognostic features, temsirolimus being

favored for patients with poor prognostic features, sorafenib being favored for patients whose disease has progressed after cytokines, and everolimus being the choice for patients whose disease has progressed after VEGF receptor (VEGFR) inhibitor therapy. However, despite these undeniable advances, there remains considerable room for improvement. These new agents have persistent nagging side effects, and produce at best partial responses that last a median of less than 12 months. Insufficient scientific information is available to help identify the optimal initial treatment or treatment sequence for an individual patient or to treat upfront refractory or acquired resistant disease. These issues represent a major focus of the DF/HCC Kidney Cancer Program and SPORE.

PI3 Kinase Inhibitors - Better than Rapalogues?

By Daniel Cho M.D. and James Mier M.D., Beth Israel Deaconess Medical Center

Until last year, the only FDA-approved targeted therapies available for the treatment of patients with metastatic kidney cancer were angiogenesis inhibitors that work by blocking the effects of vascular endothelial growth factor (VEGF). Two recent developments—the approval of temsirolimus (Torisel) and the demonstration that everolimus (RAD001) is active in kidney cancer patients—have helped open a new front in the treatment of this disease. Both of these drugs are "rapalogues" (i.e. structural analogues of rapamycin) that inhibit the kinase mTOR. mTOR functions downstream of the enzyme PI3 kinase and is thought to regulate malignant transformation by upregulating the translation of a small

group of proteins involved in growth and survival (e.g. cyclins, anti-apoptotic proteins such as survivin). Although temsirolimus and its cousin everolimus have shown promise in the treatment of kidney cancer, preclinical studies have identified a hard-wired signaling pathway that tends to limit the effectiveness of mTOR inhibitors as a class—namely the feedback activation of the PI3 kinase pathway. The activation of this signaling pathway tends to increase tumor cell growth, invasiveness, and survival, thereby undermining the antitumor efficacy of mTOR inhibitors. This potential problem may have been solved by the recent introduction of drugs that block both mTOR and PI3 kinase (e.g. the Novartis

continued on page 3

HIF2 α : Critical Factor in RCC is Target of Novel Drug Delivery Strategy

By William Kaelin, M.D., Dana-Farber Cancer Institute

Investigations within the Kaelin Lab and the Kidney Cancer Program involving genotype-phenotype correlations and preclinical models have suggested that downregulation of HIF2 α is both necessary and sufficient for the von Hippel Lindau protein (pVHL) to suppress renal carcinoma growth. This work supports the potential therapeutic value of targeting HIF2 α in this disease. Unfortunately, transcription factors such as HIF2 α are difficult to inhibit with drug-like small organic molecules. As an alternative, we plan to investigate the utility of inhibiting HIF2 α using siRNA. Recent studies suggest that siRNA can be effectively delivered in vivo when encapsulated in nanoparticles targeted to the transferrin receptor. We have initiated experiments to test whether this technology can be used to downregulate HIF2 α in VHL^{-/-} renal carcinoma lines grown orthotopically in nude mice and will attempt to develop pharmacodynamic markers, including functional imaging approaches, suitable for preclinical and subsequent clinical studies. In addition, working with Sabina Signoretti in the Kidney Cancer SPORE/Program Pathology Core, we will measure HIF2 α and transferrin receptor levels in human kidney cancer samples to assess their relationship to each other and VHL loss, the influence of acquired resistance to VEGFR blockade on their expression, as well as their prognostic significance and ability to predict benefit to standard therapies. Together this effort will lead to the conduct of a "first in man" Phase I/IB clinical trial of HIF2 α siRNA nanoparticles in patients with RCC. This protocol will be led by Dr. Toni Choueiri (DFCI) and will be supported by Calando Pharmaceuticals, the

manufacturer of the transferrin-coated nanoparticle technology. Initial components of this trial will establish the toxicity and MTD of this approach. A subsequent expansion phase will be performed in a selected patient population informed by the aforementioned laboratory experiments and will include correlative pharmacodynamic endpoints patterned after those developed in animal models. Taken together, this work, which clearly goes from bench-to bedside, should establish the safety and therapeutic potential for targeting this critical factor in VHL^{-/-} clear cell RCC using transferrin-decorated nanoparticle containing siRNA technology and lay the groundwork for future clinical development of this potentially exciting approach in patients with this disease.

Preliminary data show that participants who used either non-aspirin NSAIDs or acetaminophen at the start of the study follow-up had about 50% elevated risk of renal cell cancer. However, aspirin use was not associated with either a higher or lower risk of renal cell cancer development. Future analysis will include additional follow-up and evaluation of all types of kidney cancer. Most recent use and duration of usage before diagnosis of kidney cancer will also be evaluated.

Analgesics implicated in Kidney Cancer Risk and Prevention:

Eunyoung Cho, M.D., Brigham and Women's Hospital, and Toni Choueiri, M.D., Dana-Farber Cancer Center Institute to study further

Analgesics are one of the most commonly used drugs in the U.S. In a random dialing survey, acetaminophen, ibuprofen, and aspirin were the 3 most commonly used prescription and over-the-counter medications. Aspirin has a well-established protective effect against cardiovascular disease and colorectal cancer; however, limited epidemiologic data are available for kidney cancer. Furthermore, previous epidemiologic data point toward a positive association between analgesic use and kidney cancer risk. In fact, some analgesics such as acetaminophen may contribute to decline of renal function and elevated risk of chronic renal disease and, subsequently, to elevated risk of kidney cancer. Thus, clarification of the associations is necessary from the public health standpoint, given the popular use of aspirin and other analgesics.

Dr. Eunyoung Cho, an epidemiologist and a long-time investigator of large ongoing prospective studies; the Nurses' Health Study and Health Professionals Follow-Up Study, and Dr. Toni Choueiri, a genitourinary oncologist at DFCI have received funding from the Kidney Cancer Association and the NIH to investigate potential associations between analgesic use and kidney cancer. Drs. Cho and Choueiri will test two hypotheses: 1) whether use of aspirin and other NSAIDs is associated with a decreased risk of kidney cancer and 2) whether use of acetaminophen is associated with an elevated risk of kidney cancer. They will utilize the two large prospective studies of men and women where extensive analgesic use and medical data have been collected.

2nd Annual Patient/Survivor Regional Symposium Held 10/24/08

By David McDermott, M.D., Beth Israel Deaconess Medical Center

DF/HCC Kidney Cancer Program/Kidney Cancer Association Patient/Survivor Regional Symposium Held October 24th, 2008, the DFHCC Kidney Cancer Program and the Kidney Cancer Association (KCA) held a joint symposium for kidney cancer patients at the Hyatt Regency in Cambridge, MA. This second annual event was Chaired by Dr. David

— 2

Angiopoeitins: Alternative Angiogenic Pathway to be Inhibited in DF/HCC-led, Combination Anti-angiogenic Therapy Trial

By Michael B. Atkins, M.D. and Rupal Bhatt, M.D., Ph.D., Beth Israel Deaconess Medical Center

The DF/HCC will soon be participating in a study of a novel antiangiogenic therapy. While RCC has been shown to respond to antiangiogenic therapies, not all patients respond to the approved agents and those who respond eventually develop resistance. With support from Amgen, we plan to conduct a phase 2 study to determine the efficacy of AMG386 in combination with sunitinib in the treatment of subjects with advanced clear cell carcinoma of the kidney. AMG386 is an inhibitor of the interaction of angiopoietin 2 (Ang-2) to its receptor, Tie 2. Recent data implicate the Ang2-Tie2 pathway as an important alternative to the VEGF pathway in supporting tumor angiogenesis. In experimental cancer models the over-expression of Ang-2 resulted in enhanced tumor angiogenesis and growth. Importantly, selective antagonists of Ang-2

inhibited tumor growth in murine xenograft models, suggesting that inhibitors of Ang-2 may have therapeutic benefit in human cancers. Preliminary studies of AMG386 in combination with sorafenib in patients with RCC suggested that the combination produced considerably greater antitumor effects than would have been anticipated with sorafenib alone. Furthermore, Kidney Cancer SPORE investigators have shown that resistance to sunitinib therapy is frequently associated with rises in plasma Ang-2 levels suggesting that Ang-2 might be a factor contributing to the “angiogenic escape” that occurs with sunitinib resistance. These findings support the investigation of AMG386 in combination with sunitinib, the current standard antiangiogenic therapy for patients with RCC.

In this study, forty subjects will receive AMG386 at the soon to be established MTD together with the approved dose and schedule of sunitinib. Patients treated within the DF/HCC institutions will also undergo arterial spin labeling (ASL) MRI to assess blood flow in RCC metastatic lesions in the hopes of further credentialing this procedure as a predictive and surrogate marker for efficacy in association with antiangiogenic therapy for RCC.

PI3 Kinase Inhibitors, *continued from page 1*

compound BEZ235). BEZ235 is already in Phase I testing and in preclinical studies, has shown antitumor activity in kidney cancer clearly superior to that achieved with rapamycin. The development of this and similar agents in the treatment of kidney cancer is one of the objectives of the DF/HCC Kidney Cancer Program and of the SPORE grant that supports much of the

translational research in kidney cancer ongoing at DF/HCC institutions. We look forward to the completion of the Phase I study of BEZ235 and to subsequent studies with this and similar agents in patients with advanced renal cancer at DF/HCC institutions.

McDermott of BIDMC and attended by over one hundred people, both kidney cancer survivors and their supporters. The symposium was designed to raise awareness about recent breakthroughs in kidney cancer therapy and provide a forum for patients to learn more about future potential advances in the field.

Symposium faculty included a multidisciplinary group of physicians, nurse practitioners, nurses and social workers for Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute and Massachusetts General Hospital.

Highlights of the meeting included: recent advances in RCC therapy and novel agents in clinical trials; faculty question and answer sessions and breakout meetings with nursing experts in symptom management and supportive care.

Similar meetings are being co-sponsored by the KCA in other cities across the United States. Given the “remarkable success” of this year’s DFHCC event, plans are being laid for the 3rd Annual Meeting in October 2009.

In the News

Bob Rebello, a patient advocate for the SPORE, has continued his effort to raise money for Kidney Cancer Research by running Marathons around the world. He has completed his latest marathon in Argentina. You may learn more about his accomplishments by visiting his web site, Bob Rebello’s Worldwide Marathons to Raise Money for Kidney Cancer: <http://www.bobrebello.com/>

Awards

Rupal Bhatt, M.D., Ph.D (BIDMC) is the recipient of the Joint Developmental Research Project Award from the VHL Family Alliance and the Kidney Cancer SPORE.

Eunyoung Cho, M.D. (BWH) and **Toni Choueiri, M.D. (DFCI)** are the recipients of the Joint Developmental Research Project Award from the Kidney Cancer Association (KCA) and the Kidney Cancer SPORE. This team has also just been granted a K03 grant from the NIH for their research.

Kevin Courtney, M.D. (DFCI) is the recipient of the Genentech Fellowship (CDA) Award.

Mike Zimmer, M.D. (MGH) and **Rupal Bhatt, M.D., Ph.D (BIDMC)** are the recipients of the Pfizer Career Development Award for the Fall 2008. Both have received a one year grant.



DF/HCC Kidney Cancer Program Members:

- | | |
|--------------------------------------|------------------------|
| Atkins, Michael B., <i>Leader</i> | Marasco, Wayne A. |
| Iliopoulos, Othon, <i>Co-Leader</i> | McDermott, David F. |
| Kaelin, William G., <i>Co-Leader</i> | Michaelson, M. D. |
| Alper, Seth Leo | Mier, James W. |
| Alsop, David C. | Mueller, Peter Raff |
| Avigan, David E. | Oh, William Kyu |
| Bhatt, Rupal S. | Olumi, Aria F. |
| Bonventre, Joseph V. | Pedrosa, Ivan |
| Burstein, Deborah | Regan, Meredith M. |
| Cho, Daniel C. | Richie, Jerome Paul |
| Cho, Euryoung | Rofsky, Neil M. |
| Choueiri, Toni K. | Rosenberg, Jonathan E. |
| Dabora, Sandra L. | Ross, Robert W. |
| Frank, David A. | Shah, Jagesh V. |
| Goldberg, S. Nahum | Signoretti, Sabina |
| Haber, Daniel A. | Skates, Steven J. |
| Hirsch, Michelle S. | Stanton, Robert C. |
| Kaplan, Irving D. | Sukhatme, Vikas P. |
| Kufe, Donald W. | Wen, Patrick Yung Chih |
| Libermann, Towia Aron | Wu, Chin-Lee |
| Loughlin, Kevin R. | Zerbini, Luiz F. |
| Manning, Brendan D. | Zimmer, Michael A. |

Next edition: Summer 2009

NCI
CCC
DANA-FARBER/HARVARD CANCER CENTER
A Comprehensive Cancer Center
Designated by the National Cancer Institute

**Newsletter of the DF/HCC
Kidney Cancer Program**



Current Clinical Trials (for complete list visit our web site at www.dfhcc.harvard.edu/renalcancer)

Advanced Disease

- Vaccination of Patients with Renal Cancer with Dendritic Cell/Tumor Fusions and GM-CSF (DF/HCC 04-117). A Phase II trial for untreated patients who present with metastatic disease and primary tumor in place.
- The High-dose Aldesleukin (IL-2) "SELECT" Trial: A Trial Designed to Prospectively Validate Models of Response to High Dose IL-2 Treatment in Patients with Metastatic Renal Cell Carcinoma (DF/HCC 06-149).
- Phase II, Randomized trial of continuous Dosing Sunitinib or Bevacizumab in Sunitinib-Refractory Patients with Metastatic Renal Cell Carcinoma (DF/HCC 07-202).
- Phase II, Single arm Trial of Combination Sunitinib and Gemcitabine in Sarcomatoid and/or Poor-risk Patients with Metastatic Renal Cell Carcinoma (DF/HCC 07-212).
- An Exploratory Study Evaluating FDG-PET as a Predictive Marker For mTOR Directed Therapy with RAD 001 in Metastatic Renal Cell Cancer (DF/HCC 08-034).

- A Phase II Single Arm Study of IMC-1121B in Patients with Metastatic Renal Cell Carcinoma with Disease Progression on or Intolerance to Tyrosine Kinase Inhibitor Therapy (DF/HCC 08-068).
- Axitinib (AG-013736) as Second-Line Therapy for Metastatic Renal Cell Cancer: Axis Trial (DF/HCC 08-163).
- E2804 The Best Trial: A Randomized Phase II Study of VEGF, RAF Kinase, and MTOR Combination Targeted Therapy (CTT) with Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma (DF/HCC 08-168).
- A Phase II Trial of Bevacizumab and Temsirolimus Following Tyrosine Kinase Inhibitor Failure in Patients with Advanced Renal Cell Carcinoma (DF/HCC 08-184)
- A Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma (DF/HCC 08-219)

Adjuvant Therapy

- A Randomized, Double Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma (DF/HCC 06-225).

Laboratory Correlates

- Collection of specimen and clinical data from patients with renal cell carcinoma treated with Target Therapies (DF/HCC 06-105).
- Collection of specimen and clinical data from patients with renal cell carcinoma (DF/HCC 01-130). Tissue banking and database protocol.
- Arterial Spin Labeling Blood Flow Magnetic Resonance Imaging for the Evaluation of Response to Antiangiogenic and Targeted Therapies of Metastatic Renal Cell Carcinoma (DF/HCC 08-078).
- A Comparative Study of PET/CT versus Diagnostic CT for the Detection of Clear Cell Renal Cell Carcinoma in Presurgical Patients with Renal Masses Using Iodine-124 labeled Chimeric G250 (124I-cG250)

Contact Information:

Administrator: Aline D. Nandelstadt
Phone: 617-632-9275 Fax: 617-632-9260
E-mail: anandels@bidmc.harvard.edu