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Next edition: Winter 2009

 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)

- High Priority Trials**
- 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.
 - Phase II trial of sunitinib and AMG386 in patients with advanced RCC (DF/HCC 09-021).
 - 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 Trial of Bevacizumab and Temsirolimus Following Tyrosine Kinase Inhibitor Failure in Patients with Advanced Renal Cell Carcinoma (DF/HCC 08-184).
- 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).

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Newsletter of the DF/HCC Kidney Cancer Program

Summer 2009

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-  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: SPORE Grant Renewal and Successful Research Retreat

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

This spring the DF/HCC Kidney Cancer Program received news that our SPORE competitive renewal grant received an "outstanding" score at peer review. Thus, it is anticipated that we will receive another 5 years of funding beginning June 1, 2009. As with the initial SPORE grant, the renewal application included investigators from all the Harvard affiliated hospitals as well as the Harvard School of Public Health and featured five major projects. These projects included: 1) Clinical Correlations of WTX Inactivation in Wilms Tumor, led by Drs. Dan Haber and Miguel Rivera from MGH, 2) Targeting of HIF2α with siRNA, led by Drs. Bill Kaelin and Toni Choueiri from DFCI and Sabina Signoretti from BWH, 3) Acquired Resistance to VEGF Receptor Blockade: Underlying Mechanism and Therapeutic Options, led by Drs. Nahum Goldberg, James Mier and myself from BIDMC; 4) Targeting the PI3-Kinase/Akt Pathway in RCC led by Drs. James Mier and David McDermott from BIDMC; and 5) Adoptive Immunotherapy for Renal Carcinoma Using Dendritic Cell/tumor Fusions, led by Drs. David Avigan from BIDMC and Don Kufe from DFCI. The five projects are supported by three cores: 1) Administration, Evaluation and Planning Core led by me with the support of SPORE and Program Administrator Aline Nandelstadt; 2) Biostatistics Core led by Dr. Meredith Regan from DFCI; and 3) Tissue Acquisition, Pathology and Clinical Data Core, led by Dr. Signoretti. The SPORE application also included a description of expanded Developmental Research and Career Development Programs under the leadership of SPORE Co-PIs Drs. Othon Iliopoulos (MGH) and

Bill Kaelin, respectively. The overall goal of the DF/HCC Kidney Cancer SPORE remains the translation of laboratory and technological advances into clinical benefit for patients with kidney cancer. The successful renewal of the SPORE was only possible through the considerable efforts of numerous individuals across the DF/HCC and beyond. I know I speak for the SPORE leadership in formally thanking at this time all those who contributed to this effort. While the SPORE renewal is cause for celebration, it carries with it a tremendous responsibility. As the only NCI funded SPORE grant focused on cancers of the kidney, the NCI and the kidney cancer community is counting on the DF/HCC investigators to lead the way in kidney cancer translational research. In order to boost the launch of the new SPORE, the Kidney Cancer Program hosted a Scientific Retreat on June 5th at the Hotel Commonwealth in Kenmore Square. The Retreat was organized by Drs. Kaelin, Mier and Iliopoulos and included a full day of oral and poster presentations from Program members. Keynote addresses were presented by Drs. Kate Nathanson from UPenn and Josh Rabinowitz from Princeton. This Newsletter highlights several efforts that were discussed at the Retreat and will likely be critical components of Kidney Cancer Program and SPORE activities over the coming years. We welcome those interested in learning more about the Program, SPORE or the Retreat or in participating in future programmatic activities to check the Kidney Program Website: <http://www.dfhcc.harvard.edu/research-programs/disease-based-programs/kidney/>



Progress in Tuberous Sclerosis and Birt-Hogg-Dube Syndrome

By Elizabeth Petri Henske, MD, Brigham and Women's Hospital

In September 2008, the Henske laboratory moved to the Brigham and Women's Hospital from Fox Chase Cancer Center in Philadelphia. Dr. Henske is a medical oncologist who attended Harvard Medical School and trained in Internal Medicine and Medical Oncology at the Massachusetts General Hospital. The Henske laboratory studies tuberous sclerosis complex (TSC) and Birt Hogg Dube Syndrome (BHD), two genetic diseases associated with renal cell carcinoma. Individuals with TSC can develop tumors in many organs, including the kidney, brain, heart, lung, and skin. In the kidney, three types of lesions occur in TSC: benign blood vessel filled tumors called angiomyolipomas, which are

very common, epithelial cysts that can sometimes resemble polycystic kidney disease, and RCC, which is the least frequent renal manifestation of TSC. The TSC proteins function as inhibitors of the mammalian target of rapamycin (mTOR) kinase, linking loss of TSC function with mTOR activation and the exciting clinical progress using mTOR inhibitors as treatment for patients with RCC. The Henske laboratory studies TSC using yeast and mouse models. Birt-Hogg-Dube syndrome is associated with renal cell carcinoma, skin tumors, and lung collapse. The Henske group has found that the TSC and BHD proteins have opposing effects on fundamental biologic processes including amino acid homeostasis, suggesting that the BHD protein may

activate mTOR. This is currently being studied in a mouse model of BHD. Thus, both kidney tumors in TSC and BHD have dysregulation of the mTOR pathway. mTOR pathway inhibitors are approved for kidney cancer therapy, although more needs to be learned to optimize their efficacy. The ultimate goal of the TSC and BHD research projects is to understand the cellular mechanisms that lead to kidney cancer in these genetic diseases, in order to facilitate the development of novel therapeutic strategies and biomarkers of response to mTOR inhibitors for individuals with sporadic renal carcinomas.

Awards

Ivan Pedrosa, MD (BIDMC) is the recipient of the Harvard Catalyst Pilot Grant Award for his proposal entitled: "Magnetic Resonance Imaging as a Genomic/Proteomic Expression Correlate to Characterize Renal Cell Carcinoma."

Daniel Cho, MD (BIDMC) has received an ASCO Career Development Award for his work related to PI3-Kinase/Akt/mTOR Pathway for the Therapy of Advanced Renal Cell Carcinoma.

Othon Iliopoulos, MD (MGH) has been awarded a R01 for his project: Identification of Biomarkers for Early Detection of Renal Cell Carcinoma.

Congratulations to **Miguel Rivera, MD (MGH)** for his 2009 Early Career Physician Scientist Award from HHMI.

In the News

Please join us in extending a warm welcome to our newest Program Members: **Drs. Elizabeth Henske (BWH), Pankaj Seth (BIDMC), and Andrew Wagner (BIDMC).**

William Kaelin, MD (DFCI) has become a Co-Leader of the Program

The DF/HCC Kidney Cancer Tissue Bank: A Bridge from the Laboratory to the Clinic

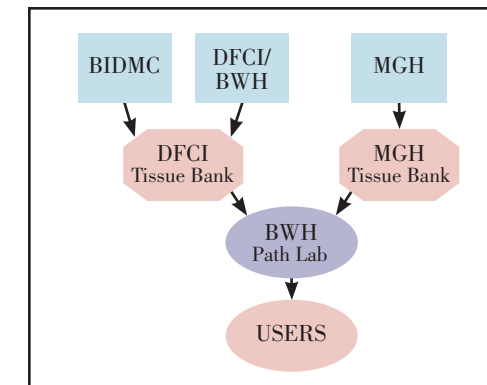
By David A. Frank, MD, PhD, Dana-Farber Cancer Institute and Sabina Signoretti MD, Brigham and Women's Hospital

The introduction of targeted therapies for the treatment of renal cell carcinoma has highlighted the importance of defining the molecular pathogenesis of this disease. Laboratory studies on the biology of kidney cancer often begin with cell lines derived from patients. However, before a laboratory advance can be translated into clinical use, it is essential that it be evaluated in tumor tissue samples taken directly from patients with kidney cancer.

While this has often been a major hurdle to making the transition from the bench to the clinic, a multi-institutional collaboration in the Kidney Cancer Program has provided an invaluable resource for translational investigators. Through the DF/HCC Kidney Cancer Tissue Acquisition, Pathology and Clinical Data Core, primary

cancer specimens are being stored for laboratory investigation, often including paired non-tumor tissue from the same patient. There are currently 1676 patients who have consented to the DF/HCC Kidney Cancer specimen banking protocol, including 926 patients from DFCI/BWH, 402 from BIDMC, and 348 from MGH. All of these patients have given their consent to link the specimens to their clinical information. OCT embedded frozen tissue is available on 668 patients. Of the 1676 consented patients, 1225 have at least one blood sample and 804 have at least one urine sample stored in the specimen bank.

Investigators requesting these samples require an IRB-approved protocol, and must submit a brief description of their plans to the multi-disciplinary Core Utilization



Tissue sample distribution to users. Tissue specimens are stored at either DFCI or MGH. Tissue specimens' quality is checked by Core Pathologists at BWH prior to distribution to Investigators.

Committee. Investigators are also asked to provide a brief progress report summarizing the findings generated from the material provided. Ultimately, the goal of the tissue bank is to utilize this invaluable resource provided by patients to enhance our understanding of the molecular pathogenesis of renal cell cancer and facilitate the translation of this enhanced knowledge into clinical application.

Sphingosine 1 Phosphate - A novel target for kidney cancer?

By Rupal Bhatt, MD, PhD, Beth Israel Deaconess Medical Center

The approval of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) has provided new options for many patients with metastatic kidney cancer. However, within one year, the majority of patients become resistant to these agents. We have been studying the mechanisms by which tumors develop resistance to the VEGFR TKIs, sorafenib and sunitinib. Although recent studies show that everolimus can provide benefit in this situation, this is typically limited to only a few months. Better therapies to treat VEGFR TKI resistant disease are greatly needed. We have found that sphingosine kinase (Sphk), an enzyme that catalyzes the production of the bioactive sphingolipid sphingosine 1-phosphate (S1P), is increased when tumors become resistant to sunitinib. S1P has recently been proposed as a novel target for cancer therapy in other tumors based on its

ability to promote angiogenesis and tumor progression. An antibody that neutralizes the activity of S1P is currently being developed by our collaborators at Lpath, Inc. This antibody has shown antitumor activity in various mouse tumors models and we have tested this antibody in a mouse model of kidney cancer. We have found that this antibody slows tumor growth and are currently testing its activity in sunitinib resistant tumors. The human form of this antibody is being developed by Lpath Inc and this agent, ASONEP, is currently being evaluated in phase I clinical trials. Thus, S1P antagonism may be a novel therapy for kidney cancer that may be particularly useful in patients who develop resistance to VEGFR TKIs. We anticipate launching clinical studies with ASONEP in patients with RCC in the coming months.

DFHCC Clinical Trials Update

By David McDermott, MD, Beth Israel Deaconess Medical Center

Adjuvant RCC Trial Extends Enrollment

The ASSURE Trial, a Randomized, Double-Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected RCC remains open to enrollment at the DF/HCC (ECOG 2805). This NCI sponsored, Intergroup trial is designed to demonstrate an improvement in disease-free survival in locally advanced RCC patients following nephrectomy. While the trials' planned sample size was large (1332 patients) and it is currently accruing ahead of schedule, the large number of patients who have come off therapy due to intolerance of side effects has necessitated an increase in the accrual goal to 1923 patients.

Eligible patients will be stratified based on stage, histology, performance status and

type of nephrectomy and then randomly assigned to adjuvant Sunitinib (Arm A) or Sorafenib (Arm B) or Placebo (Arm C) following radical or partial nephrectomy. Since there is no known effective adjuvant therapy for RCC, a positive result would change clinical practice. Patients may enroll before or within 10 weeks following nephrectomy.

Salvage trials designed to treat TKI resistant RCC

The recent revolution in the therapy for metastatic RCC has created a new therapeutic dilemma. How do you treat a patient who develops disease progression while receiving a VEGF receptor tyrosine kinase inhibitor (TKI)? Investigators at DFHCC are studying several approaches to this increasingly common clinical situation.

1) Switch to a different agent AXIS Trial

A Phase III trial of axitinib versus sorafenib in sunitinib failures. This trial will examine the role of axitinib, the VEGF TKI with the most promising Phase II activity compared to a current standard of care, switching to sorafenib, in patients with disease progression on sunitinib.

Everolimus in RCC with PET Predictive Marker

A Phase II trial of Everolimus in patients who have failed prior VEGFR TKI therapy. This study will examine the value of PET scan as a predictive marker of disease response to mTOR inhibition using what is a standard care for this patient population.

2) Switch to a combination therapy Avator Trial

A single arm, Phase II trial of the combination of bevacizumab and temsirolimus in patients with mRCC who have progressed on VEGF TKI therapy.