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Kidney Cancer: Opportunity for Disease Specific Targeted Therapy

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Kidney cancer affects nearly 39,000 Americans every year and is responsible for nearly 13,000 deaths per year in the U.S. Sixty percent of patients affected with this disease present clinically with either locally advanced or systemic disease. Kidney cancer, like most solid malignancies, is nearly always fatal when a patient develops advanced disease. Historically, only eighteen percent of patients who present with metastatic kidney cancer survive twenty four months. While there have been significant advances and long term complete responses in patients treated with interleukin-2 based therapies, most patients do not respond to this form of therapy.

The current approaches for molecular therapy for kidney cancer are based on work that began 25 years ago to identify the disease genes for cancer of the kidney. The fundamental aspect of targeting the kidney cancer disease genes comes from an understanding that kidney cancer is not a single disease, it is made up of a number of different types of cancer; each with a different histologic type, a different clinical course, responding differently to therapy and caused by a different gene. What has been learned about the genetic basis of kidney cancer has come from the study of families affected with inherited forms of the disease. The study of these four different types of kidney cancer has lead to the identification of 4 genes that cause kidney cancer. The VHL gene is the gene for sporadic, clear cell renal carcinoma as well as the inherited form of clear cell renal carcinoma associated with von Hippel Lindau, the c-Met gene is the gene for the inherited form of type 1 papillary kidney cancer found in Hereditary Papillary Renal Carcinoma, the BHD gene is the gene for Birt-Hogg-Dubé (chromophobe kidney cancer) and fumarate hydratase (FH) is the gene for Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC).([1])

It is remarkable testament to the single minded focus of a large number of clinical as well as basic scientists, that only 13 years after discovery of the first kidney cancer gene, the VHL gene, the FDA approved two drugs for kidney cancer (sunitinib and sorafenib) which target the VHL pathway. A third drug, which also targets the MTOR/HIF pathway, temsilorimus, is likely to be approved soon. Intense efforts are currently underway to develop agents which target the c-Met gene, for type 1 papillary kidney cancer; the BHD gene, for chromophobe kidney cancer; and the fumarate hydratase pathway for type 2 papillary renal cell carcinoma.

In an elegant summary of where the field stands now, Rini and Flaherty describe both the rationale for use as well as the current clinical results and potential future approaches for molecular therapeutics in kidney cancer with agents such as sunitinib, sorafenib, temsilorimus and bevacizimab.(2) They also detail the opportunities as well as the challenges ahead in the quest to develop an effective form of therapy for all patients with kidney cancer. Klatte, et al. provide an updated assessment of the surveillance strategy developed on the basis of the University of California Integrated Staging System (UISS).([3]) These investigators have not only continued to refine their integrated prognostic model and have incorporated molecular markers to provide improved tools and rationale management/surveillance of patients with localized kidney cancer but also have provided an invaluable foundation for determining which

patients are most likely to benefit from targeted molecular therapeutic approaches to the treatment of patients with recurrent kidney cancer.

Reference List

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