Published in final edited form as:
Semin Oncol. 2013 August ; 40(4): 511–520. doi:10.1053/j.seminoncol.2013.05.009.

Non-Clear Cell Renal Cancer: Disease-Based Management and Opportunities for Targeted Therapeutic Approaches

W. Marston Linehan[1,*], **Ramaprasad Srinivasan**[1], and **Jorge A. Garcia**[2]

Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda Maryland Solid Tumor Oncology Department, Taussig Cancer Institute Cleveland Clinic, Cleveland, Ohio

Abstract

A better understanding of the biology of renal cell carcinoma (RCC) has significantly changed the treatment paradigm of the disease. Several novel VEGF and TORC inhibitors have bee recently FDA-approved. Unfortunately, the vast majority of clinical trials conducted today have been aimed to include patients with clear-cell RCC which remains the most common histologic subtype of the disease. Non-clear cell RCC represents approximately 20 to 25% of all RCC patients. Non-clear RCC is made up of multiple histologic subtypes each with a different molecular printing profile. Although VEGF and TORC inhibitors are commonly used in the management of this cohort of patients, non-clear cell histologies do not appear to be related to VHL. As such the clinical efficacy of the existing agents is quite limited. There is a need to develop more rational therapeutic approaches that specifically target the biology off each of the different subtypes of non-clear RCC. In this review, we discuss molecular and clinical characteristics of each of the non-clear cell RCC subtypes and describe ongoing efforts to develop novel agents for this subset of patients.

Introduction

Renal cell carcinoma (RCC) is not a single disease; it is made up of a number of different types of cancer, each with a different histology, a different clinical course and caused by a different gene. Clear cell RCC represents approximately 75% of renal cancers. Non-clear cell RCC is made up of a diverse group of histologic types including type 1 papillary renal cancer, TFE3 kidney cancer, type 2 papillary renal cancer, fumarate hydratase and succinate dehydrogenase associated renal cancer, chromophobe kidney cancer, collecting duct carcinoma and medullary RCC. The discovery of the *VHL* gene in 1993[1] was a seminal event in the effort to develop an effective form of therapy for clear cell kidney cancer. Although seven novel therapeutic agents that target the *VHL* gene pathway have been approved for treatment of patients with advanced RCC, the effectiveness of these agents in non-clear cell RCC is not well defined. While advances in genomics and large scale approaches such as The Cancer Genome Project hold great promise for identification of the

[*]Correspondence W. Marston Linehan, M.D., Urologic Oncology Branch, National Cancer Institute, 10 Center Drive MSC 1107, CRC Room 1W-5940, Bethesda, Maryland 20892-1107, Office: (301) 496-6353, Fax: (301) 402-0922, WML@nih.gov.

genetic basis of non-clear cell RCC, much of the insights that have been gained to date about the genetic basis of non-clear cell RCC have come from the study of the inherited forms of these diseases. Figure 1

Type 1 Papillary Renal Cancer

Papillary RCC is often divided into type 1 papillary RCC and type 2 papillary RCC. Type 1 papillary RCC occurs in both a sporadic as well as an inherited, familial form. Sporadic type 1 papillary RCC is most often multifocal, often with a single dominant mass with multiple small, “incipient” lesions (“papillary adenomas”) found in the adjacent renal parenchyma. Patients affected with type 1 papillary RCC can present with bilateral, multifocal disease. Type 1 papillary RCC tends to be hypovascular on imaging[2] and may be characterized by slow growth. It is most often less likely to metastasize than clear cell RCC. Surgical resection remains the standard of care for patients with localized type 1 papillary RCC.

Hereditary Papillary Renal Carcinoma: Type 1 Papillary Kidney Cancer

Hereditary Papillary Renal Carcinoma (HPRC) is a rare hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal type 1 papillary RCC. [3](3) HPRC is highly penetrant; affected individuals have nearly a 90% chance of developing RCC by the 8th decade. [4] It is estimated that patients affected with HPRC are at risk for the development of up to 1100 tumors per kidney. [5] The management of HPRC-associated RCC cancer involves active surveillance of small renal tumors; surgical intervention is recommended when the largest tumor reaches the 3 cm threshold.[6]

The Genetic Basis of Type 1 Papillary Renal Cell Cancer

Genetic linkage studies performed in HPRC families localized the HPRC gene to the long arm of chromosome 7 and identified *MET*, the cell surface receptor for hepatic growth factor (HGF) as the gene for Hereditary Papillary RCC.[7] Activating mutations in the tyrosine kinase domain of the *MET* gene are found in the germline of HPRC patients. Although MET is commonly amplified in type 1 papillary RCC, *MET* mutations have been identified in only a subset (13%) of tumors from patients with sporadic, non-hereditary papillary RCC. Although MET gene amplification is thought to play a critical role in the pathogenesis of this disease, the genetic basis of the majority of sporadic type 1 papillary RCC remains to be determined.

Targeting the MET pathway in Papillary Renal Carcinoma

There are currently no systemic agents of proven clinical benefit in patients with advanced papillary RCC (or other non-clear cell variants). Patients with unresectable disease requiring therapy usually receive either an mTOR inhibitor or a VEGF pathway antagonist, based on demonstration of modest activity in several retrospective analyses, small single arm phase 2 studies, and at least one subgroup analysis of a large randomized phase 3 study. In most studies, objective response rates following therapy with mTOR or VEGFR-targeted TKIs were low (0–36%), with a median progression free survival (PFS) of less than 6 months.[8–14] Inhibitors of the epidermal growth factor receptor (EGFR) have also been evaluated in

papillary RCC; in a phase 2 trial of the EGFR inhibitor erlotinib, the overall response rate in 52 patients with metastatic papillary RCC was 11%, with a 6 month PFS of only 29%.[15]

The identification of oncogenic *MET* mutations in patients with HPRC as well as in a subset of patients with sporadic papillary RCC has led to considerable interest in targeting the HGF/MET pathway in these malignancies. Foretinib (formerly XL880), an inhibitor of Met, VEGFR2, RON and AXL tyrosine kinases was one of the earliest agents targeting the Met pathway available for clinical investigation. In a recently concluded multicenter phase 2 study, two dosing schedules of foretinib were evaluated in patients with papillary RCC.[16] A total of seventy-four patients were enrolled sequentially into one of two independent cohorts to receive either: A) an intermittent dosing regimen (240mg/d PO days 1–5 of every 14-day cycle, N=37) or B) a daily dosing regimen (80mg/d PO, N=37). The overall response rate in the entire cohort was 13.5%, with 10/75 patients experiencing a partial response. The median PFS was 9.3 months, considerably higher than that seen in historical controls treated with agents targeting VEGFR or mTOR pathways. The clinical activity of foretinib was most pronounced in patients with germline mutations in *MET;* in a preplanned subgroup analysis, 5/10 (50%) of patients with germline *MET* mutations experienced a PR, while only 5/57 (9%) of patients without this alteration had an objective response. Patients with papillary type 1 as well as those with type 2 tumors were enrolled on this study. Although central pathology review of all tumors was conducted to confirm papillary histology, sufficient tumor was not available in several instances to render an accurate subclassification; it was, therefore, not possible to determine if the type 1 and type 2 papillary tumors exhibited differential sensitivity to foretinib. The adverse event profile associated with this agent was reminiscent of that seen with other inhibitors of the VEGF axis. However, a higher than anticipated incidence of pulmonary thromboembolism (11%) was noted, as were alterations in dark adaptation in several patients treated on this trial. These data suggest that Met pathway antagonists are worthy of further study at least in some subgroups of papillary RCC. At least one other Met inhibitor, tivantinib (ARQ197), is currently undergoing evaluation with or without erlotinib in a randomized phase 2 trial in patients with advanced papillary RCC. (NCT01688973)

MiT family Renal Cancer: TFE3, TFEB and MITF

In 1996 a novel type of translocation RCC was described involving TFE3, a member of microphthalmia transcription factor/ transcription factor E (MITF-TFE) family of basic helix-loop helix leucine zipper (bLHL-Zip) transcription factors.[17,18] In the initial report, a t(X;1)(p11.2;q21.2) translocation in papillary RCC was described involving the gene *PRCC* to the *TFE3* transcription factor. Since the original description of TFE3 kidney cancer, a number of other *TFE3* fusion partners such as *NonO-TFE3, PSF-TFE3, CLTC-TFE3* and *ASPL-TFE3* have been described.[19–21] In 2003 Davis, et al. described the *Alpha-TFEB* fusion in renal tumors harboring the t(6;11)(p21;q13) chromosome translocation.[22] Bertolotto et al. recently identified germline mutations in MITF, a third member of the MiT transcription factor family, in families at increased risk for the development of RCC and melanoma.[23]

Xp11.2 translocation/TFE3 fusion RCC occurs predominantly in children and young adults. It represents 1–1.6% of all renal tumors, 15% of kidney tumors in patients under 45 years of age and 20–45% of kidney cancers in children and young adults.[24] These tumors, which are most often associated with an early age of onset, are aggressive and have a propensity towards early nodal metastasis. The treatment of localized disease is surgical and includes lymph node resection.

Treatment of Advanced TFE3 Kidney Cancer

Optimal therapy for unresectable translocation RCC remains under investigation. At least two case series have evaluated the role of VEGF-pathway antagonists in this disease. In a retrospective study of 15 patients with translocation RCC (diagnosed by either histological/ imunohistochemical features or demonstrable translocation involving chromosome Xp11.2), who were treated with one of a variety of inhibitors of the VEF axis, three partial responses and seven patients with stable disease were noted. Median PFS and OS were 7.1 months and 14.3 months respectively. Investigators from the French Juvenile RCC Network reported their experience in twenty one patients with metastatic TFE3 tumors treated with systemic therapy.[25] Four of eleven patients receiving sunitinib in the first line setting had an objective response, with a median PFS of 8.2 months. Responses were also seen in patients receiving this agent as well as those receiving an mTOR inhibitor as salvage therapy following failure of first line agents.

In a recent publication, Tsuda et al suggested that activation of the Met pathway was one consequence of the aberrantASPL-TFE3 fusion product, leading to the evaluation of Met antagonists in MiTF associated tumors. [26] However, in a phase 2 study of the allosteric Met inhibitor tivantinib in patients with Microphthalmia Transcription Factor-associated tumors, none of the six RCC patients treated demonstrated an objective response, with a disappointing median PFS of 1.9 months. [27] Further studies are required to validate Met as a viable therapeutic target in TFE3 tumors. Several laboratories are currently studying the molecular mechanisms underlying this RCC variant in a bid to uncover other pathways that may be amenable to pharmacologic modulation.

Type 2 Papillary Renal Cancer

Type 2 papillary kidney cancer is made up of a number of different of non-type 1 papillary RCC, including Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) kidney cancer.

Hereditary Leiomyomatosis renal cell carcinoma: Type 2 papillary kidney cancer

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyomas and RCC. [28, 29] The cutaneous leiomyomas may appear as raised, reddened lesions that can occur in clusters on the trunk, limbs or face. [30] The uterine leiomyomas are highly penetrant, can be multiple and are early onset (third decade). [31] HLRCC is characterized by germline mutation of the Krebs cycle enzyme gene, fumarate hydratase. [32–34] Patients affected with HLRCC are at risk for the development of

renal cysts and a very aggressive form of type 2 papillary RCC. [35, 36] HLRCC-associated kidney cancers can be bilateral and/or multifocal and can form inside renal cysts. Whereas HPRC tumors, which are type 1 papillary kidney cancer, tend to be encapsulated and slow growing, HLRCC renal tumors have a tendency to infiltrate deeply into the renal parenchyma and can spread when the tumors are very small (1/2 cm). [35] Management of localized HLRCC-associated kidney cancer involves surgical resection of localized tumors. Active surveillance is not recommended for HLRCC-associated kidney cancers and surgical treatment involves wide excision of localized tumors. Partial nephrectomy is recommended when feasible as these patients have a life-long risk for the development of bilateral, multifocal kidney tumors.

Hereditary leiomyomatosis and RCC is characterized by germline mutation of the Krebs cycle enzyme gene, *fumarate hydratase* (FH). [32–34] *Fumarate hydratase* is a loss of function, two-hit tumor suppressor gene; loss of the second FH allele is detected in HLRCC-associated kidney cancer. Fumarate hydratase-deficient RCC is prototypic example of the Warburg effect in cancer. In FH-deficient RCC oxidative phosphorylation is significantly impaired and the cancer cells undergo a metabolic shift to aerobic glycolysis for ATP production. [37, 38] Inactivation of fumarate hydratase results in an increase in fumarate which impairs prolyl hydroxylase function, leading to stabilization of HIF1α. [39] Increased glycolysis suppresses AMPK[38] and FH-deficient kidney cancer cells shift to reductive glutamine dependent pathway to support the increased lipid biosynthesis required by these rapidly proliferating cells. [40]

Therapeutic Approaches for Advanced HLRCC Kidney Cancer

HLRCC-associated kidney cancer is a most aggressive form of type 2 papillary RCC. These tumors can spread when they are very small and tend to progress rapidly. Therapeutic approaches are intended to target the metabolic shift to aerobic glycolysis and to take advantage of these cells' need for increased vasculature and increased dependence on glucose for energy production in rapidly proliferating cells. Investigators from the National Cancer Institute (NCI) are evaluating the efficacy combined VEGF and EGFR blockade in HLRCC, based on the premise that this combination will impair blood flow and glucose delivery to tumor cells. A recent retrospective analysis outlined the outcomes of eighteen patients with advanced HLRCC associated kidney cancer treated with systemic therapy during a ten-year period (1998–2008). [41, 42] Seven patients were treated with combined VEGF/EGFR inhibition while 11 patients received a variety of other standard agents including cytokines, VEGFR inhibitors, and mTOR inhibitors. Patients treated with concomitant VEGF/EGFR blockade had an ORR of 71% (5/7), including one patient with a complete response (14%) and 4 patients with a partial response (57%). Responses were durable, with one patient remaining disease free 74 months after treatment initiation. Combined VEGF/EGFR blockade resulted in significantly improved overall survival compared to other treatment regimens (median 51 months vs. 14 months; P=0.0012). Based on these data, a phase 2 trial is currently underway at the NCI to evaluate the role of bevacizumab and erlotinib in patients with advanced HLRCC-associated kidney cancer (NCT01130519).

Succinate dehydrogenase kidney cancer (SDH-RCC)

Succinate dehydrogenase kidney cancer (SDH-RCC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of pheochromocytomas, paragangliomas and RCC. [43, 44] These patients are characterized by germline mutations of the *SDHB*, *SDHC* or *SDHD* genes. [44–50] Patients affected with SDH-RCC can develop oncocytic renal tumors, clear cell or papillary RCC. SDH-RCC can be an aggressive form of RCC which has the potential to metastasize when the tumors are small. Management of localized SDH-RCC associated kidney tumors involves surgical resection when the kidney tumor is detected. Active surveillance of small SDH-RCC renal tumors is not recommended. [41]

Succinate dehydrogenase is a mitochondrial multimeric complex, comprised of the SDHA, SDHB, SDHC and SDHD subunits that serves a dual role as a Krebs (TCA) cycle enzyme as well as forming a critical function in the electron transport chain (complex 2). [51] SDH-RCC is an example of the Warburg effect in cancer; mutation of *succinate dehydrogenase* impairs oxidative phosphorylation and the kidney cancer cells undergo a metabolic shift to aerobic glycolysis. When succinate dehydrogenase is deficient, succinate accumulates and the increased succinate inhibits cytosolic HIF-α prolyl hydroxylase, resulting in accumulation of HIF1α. [52] The resulting increase in HIF1α leads to increased transcription of vascular endothelial growth factor (VEGF) the glucose transport gene, GLUT1, which would provide increased vascularity and glucose to the rapidly growing, glucose dependent SDH-deficient kidney cancer. Therapeutic trials involving approaches targeting the vascularity and glucose dependence of SDH-RCC will be initiated in the near future.

Chromophobe Renal Cell Carcinoma

Chromophobe RCC, which was described by Thoenes, et al. in 1985,[53] occurs in 4% of all cases of kidney cancer. While TNM stage groupings and sarcomatoid differentiation are significantly associated with cancer specific survival,(54) chromophobe RCC is most often detected when it is localized to the kidney. Chromophobe RCC is slow growing and tends to be less likely to metastasize than are, for example clear cell and type 2 papillary RCC, with fewer than 5% of patients presenting with advanced disease. [54, 55] The genetic basis of sporadic chromophobe RCC is not known, however, study of the inherited from of chromophobe RCC associated with Birt-Hogg-Dubé has provided insights into potential approaches for therapy of this disease.

Hereditary Chromophobe Renal Cell Carcinoma: Birt-Hogg-Dubé

Birt-Hogg-Dubé (BHD) is an autosomal dominant hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous fibrofolliculomas,[56] pulmonary cysts[57] and RCC. [58] Patients affected with BHD are at risk for the development of bilateral, multifocal renal tumors. BHD tumors may be chromophobe, hybrid oncocytic or clear cell RCC. [59] Surgical management of localized BHD-associated RCC involves active surveillance of renal tumors until the largest tumor reaches the 3 cm threshold, at which time surgical intervention is recommended.

Therapeutic Approaches for BHD Associated Kidney Cancer: Targeting the FLCN Gene Pathway

The BHD gene, *FLCN*, is located on the short arm of chromosome 17. [60,61] Inactivating mutations of the *FLCN* gene have been detected in the germline of over 95% of BHD families. [61,62] *FLCN* is a two-hit, loss of function tumor suppressor gene. Mutation or loss of the somatic *FLCN* allele is detected in 70% of BHD-associated kidney tumors. [62](62) FLCN is in the AMPK/TSC/mTOR pathway. (Figure 2) The product of the *FLCN* gene, folliculin, binds two novel proteins, FNIP1 and FNIP2, which bind the γ-subunit of the energy sensing protein complex, AMPK.[63,64] Inactivation of *FLCN* results in activation of mTORC1 and mTORC2.[63, 65] In order to evaluate the role of agents targeting the *FLCN* pathway, a murine model in which *FLCN* was specifically knocked out in the kidney was developed. In the kidney targeted *FLCN* knockout mouse model the affected mice develop cystic kidneys and renal insufficiency. Treatment of the *FLCN* knockout mice with an agent which targets the mTORC1 pathway (rapamycin) had a significant effect on the renal phenotype and doubled the life expectancy of the animals. [66] Understanding the *FLCN* gene pathway has provided the foundation for the development of a targeted therapeutic approach for the treatment of BHD-associated kidney cancer.

Tuberous sclerosis complex: TSC1/2

Tuberous sclerosis complex (TSC) is a hereditary hamartoma syndrome in which affected individuals are at risk for the development of multisystem manifestations, including neurologic dysfunction and CNS tumors, cutaneous angiofibromas, pulmonary lymphangiomyomatosis and renal tumors. [67] TSC-associated renal tumors are predominantly angiomyolipomas; however, TSC patients are also at risk for the development of clear cell, papillary and chromophobe RCC. [67, 68]

The knowledge that TSC1/2 genes are in the LKB1/AMPK/TSC/mTORC1 pathway has provided the foundation for the development of rational approaches for TSC-associated renal tumors. [69] In a first step in the development of a therapeutic approach for TSC-associated renal tumors Bissler, et al. reported shrinkage of TSC renal tumors with treatment with rapamycin. [70]

Collecting Duct and Medullary Renal Cell Carcinoma

Collecting Duct

Collecting duct RCC (CDRCC) is a rare pathological entity that comprises less than 2% of cases of kidney cancer. The prognosis of patients with CDRCC is quite poor. As such, early histological identification is important. [71, 72] This type of RCC is thought to arise from the collecting ducts in the renal medulla. Typically, CDRCC has a tubular or tubulo-papillary growth pattern that infiltrates the renal parenchyma and is associated with a desmoplastic stroma. CDRCC usually display high grade (Fuhrman 3 and 4) nuclear features. [73, 74] Most of the existing data about systemic treatment of this histologic RCC variant comes from case reports, retrospective studies and small subset analysis of RCC clinical trials where histology was not restricted to clear-cell only. Recently Wright and colleagues[75] evaluated the effect of collecting duct histology on RCC outcome using the Surveillance,

Epidemiology and End Results (SEER) data based program from 2001 to 2005. Only 160 CDRCC cases were identified during that period of time. Similar to previous reports, high rates of bulky disease (pT3 or greater) and nodal involvement were noted. [76, 77] Although the rates of nephrectomy appeared to be similar to those with clear cell RCC (84% and 78%, p=0.06), the 3-year disease-specific survival rates were greater for patients with clear cell histology. In fact, there was an increase in mortality for those patients with CDRCC histology (HR 2.42, 95% CI 1.72–3.39, p=0.001).(75) Previous reports by Motzer and colleagues also demonstrate that regardless of treatment received less than 5% of patients with CDRCC, survive past 2 years. [78]

Most patients with localized or locally advanced disease CDRCC are found at the time of nephrectomy. The optimal systemic management for patients with advanced disease remains unknown. Multiple case reports have indicated modest response when cytokines are used. [79] The role of VEGF or mTOR inhibitor in the management of this disease is not defined. Several reports however indicate the lack of robust clinical activity of any of the available agents. [14, 80] Despite of its histological heterogeneity, CDRCC appears to overlap with urothelial carcinomas. Thus, many clinicians have adopted cisplatin-based chemotherapy as a routine regimen in the management of these complex patients. [81, 82] Recently, Oudard and colleagues from the GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales) reported the first prospective multicenter phase II study evaluating cisplatin-based chemotherapy in patients with advanced CCDRCC. [83] Although this study was closed early secondary to poor accrual, all 23 patients enrolled on trial had central pathologic review. Patients received cisplatin (70 mg/m2) on D1 and Gemcitabine (1,250 mg/m2) on D1 and D8 of each 3-week cycle. Cisplatin was replaced by Carboplatin (AUC 5) in patients with impaired renal function (estimated creatinine clearance 30–60ml per minute per m2). Patients received a median of 6 cycles of therapy (range 1–8). Carboplatin was given to 5 (22%) patients. Patients experienced adverse events (AEs) typically seen with this regimen. ORR was 26% (95%CI 8 to 44) with one RECIST-defined CR and five PRs; 44% of patients achieved stable disease (SD). The median PFS and OS were 7.1 (95% CI 3 to 11.3) and 10.5 months (95% CI 3.8 to 17.1), respectively.

Medullary Carcinoma

In 1996 Davis, et al. described the presence of a rare form of kidney cancer, renal medullary carcinoma (RMC), in thirty three patients, all of whom were affected with sickle cell trait or hemoglobin SC disease. [84] These patients were of African descent and tended to be young (between the ages of 11 and 39 years). RMC is an extremely lethal disease, with a mean survival of only 15 weeks (range 2 to 52) after surgery. [84, 85] While this disease may be treated successfully by surgical resection if detected early,[86] advanced disease remains resistant to treatment, including cytokine therapy or chemotherapy. [87] Unfortunately up to 95% of patients have metastatic disease at the time of diagnosis. In 2006 Ronnen, et al. reported a single patient with renal medullary carcinoma who was disease free twenty-seven months after a 7 month course of treatment with bortezomib. [87, 88] Others have evaluated the role of cytotoxic therapy with methotrexate, vinblastine, Adriamycin and cisplatin (MVAC). Despite of these encouraging reports, the prognosis of patients with advanced RMC is quite poor. [89] Multiple studies evaluating the gene expression profiling of medullary RCC have

failed to demonstrate an association with clear cell or papillary histologies and suggest a unique and independent biology distinct from other forms of RCC.[90] Of interest, however is the overexpression of DNA topo II α often found in medullary RCC. This finding if often used to support the clinical use of Topo II inhibitors such as doxorubicin and etoposide in the management of this disease. [91] Although standard of care for this disease has not been clearly defined, the vast majority of advanced RMC receive cytotoxic chemotherapy. There is no data to support the use of VEGF or mTOR inhibitors in this histologic variant of RCC.

Ongoing Clinical Trials for Non-Clear Cell RCC

Several clinical trials are currently evaluating a wide range of therapeutic approaches in patients with non-clear cell RCCs. Since many of these RCC variants are relatively uncommon entities, most trials are not subtype specific. The activity of everolimus monotherapy in advanced papillary RCC is currently being investigated in an ongoing phase II, single arm, multicenter, European trial (NCT00688753). Two randomized phase 2 trials comparing everolimus with sunitinib in previously untreated patients with advanced non clear cell RCC are currently accruing patients (NCT 01185366 and NCT 01108445), while a Korean phase II study evalauting single agent pazopanib in this population (NCT01538238) is expected to commence accrual soon. Lastly, combinations of bevacizumab with erlotinib (NCT01130519) or with everolimus (NCT01399918) are also being evaluated in papillary RCC patients. It is hoped that these relatively large phase 2 studies will shed further light on the activity of VEGF and mTOR pathway antagonists in pRCC.

Conclusion

Non-clear cell RCC is a heterogeneous group of cancers that encompasses multiple histologies with different molecular features. Although inhibition of the mTOR and VEGF signaling pathways might lead to some clinical benefit, this is often marginal and prognosis remains poor. Surgery for those with localized or locally advanced disease remains the initial and more important approach. For patients with advanced disease, a clinical trial should be considered when available. With the limitations in sample size and slow accrual, the aim of future studies should be based on the biology of the disease.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. The authors thank Georgia Flaten Shaw for the outstanding editorial and graphics support.

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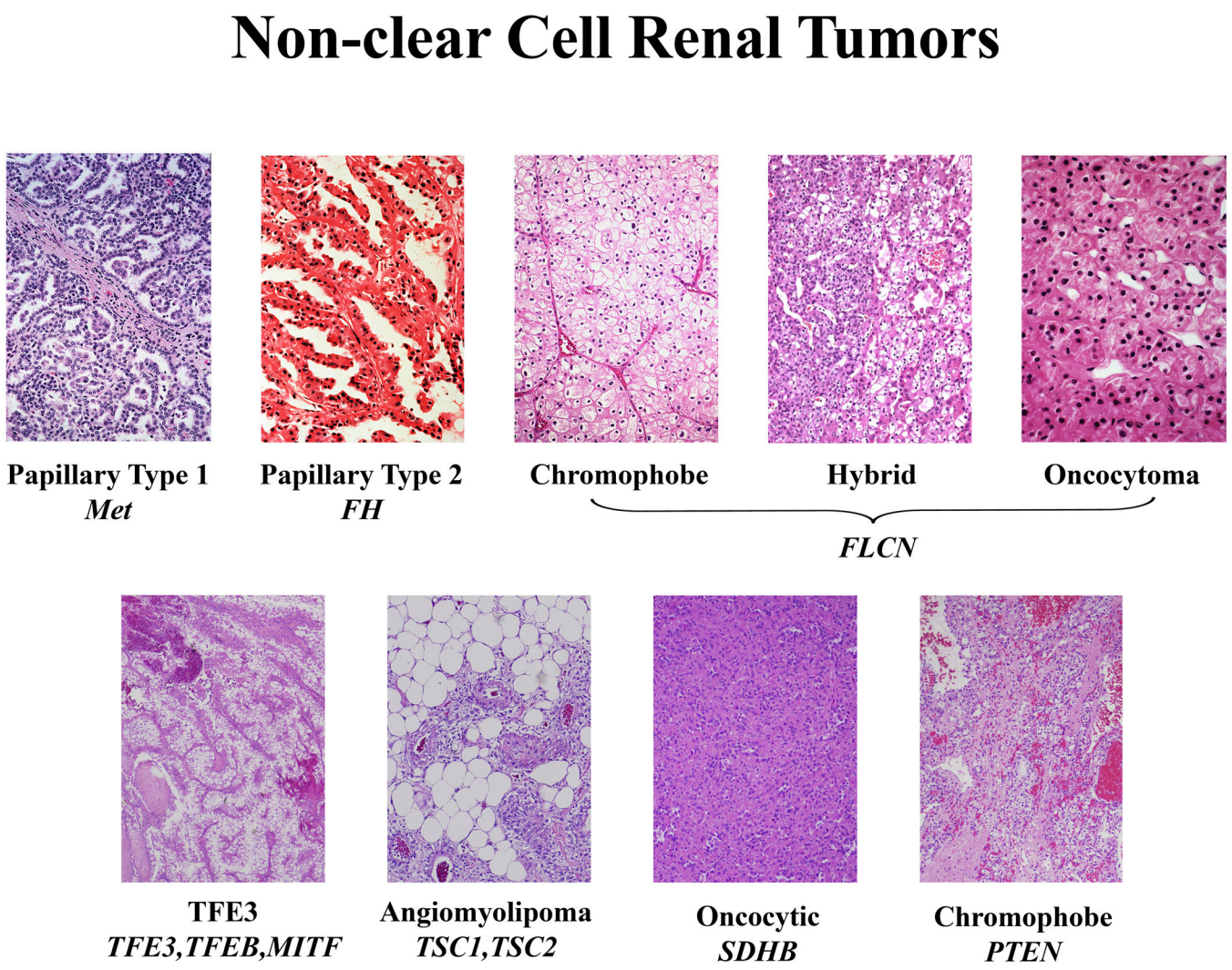

Figure 1. Non-Clear Cell Kidney Cancer

Non-clear cell kidney cancer is not a single disease, it is made up of a number of different types of cancer, each with a different histology, a different clinical course, responding differently to therapy and caused by a different gene. Adapted from Linehan, 2012 (88)

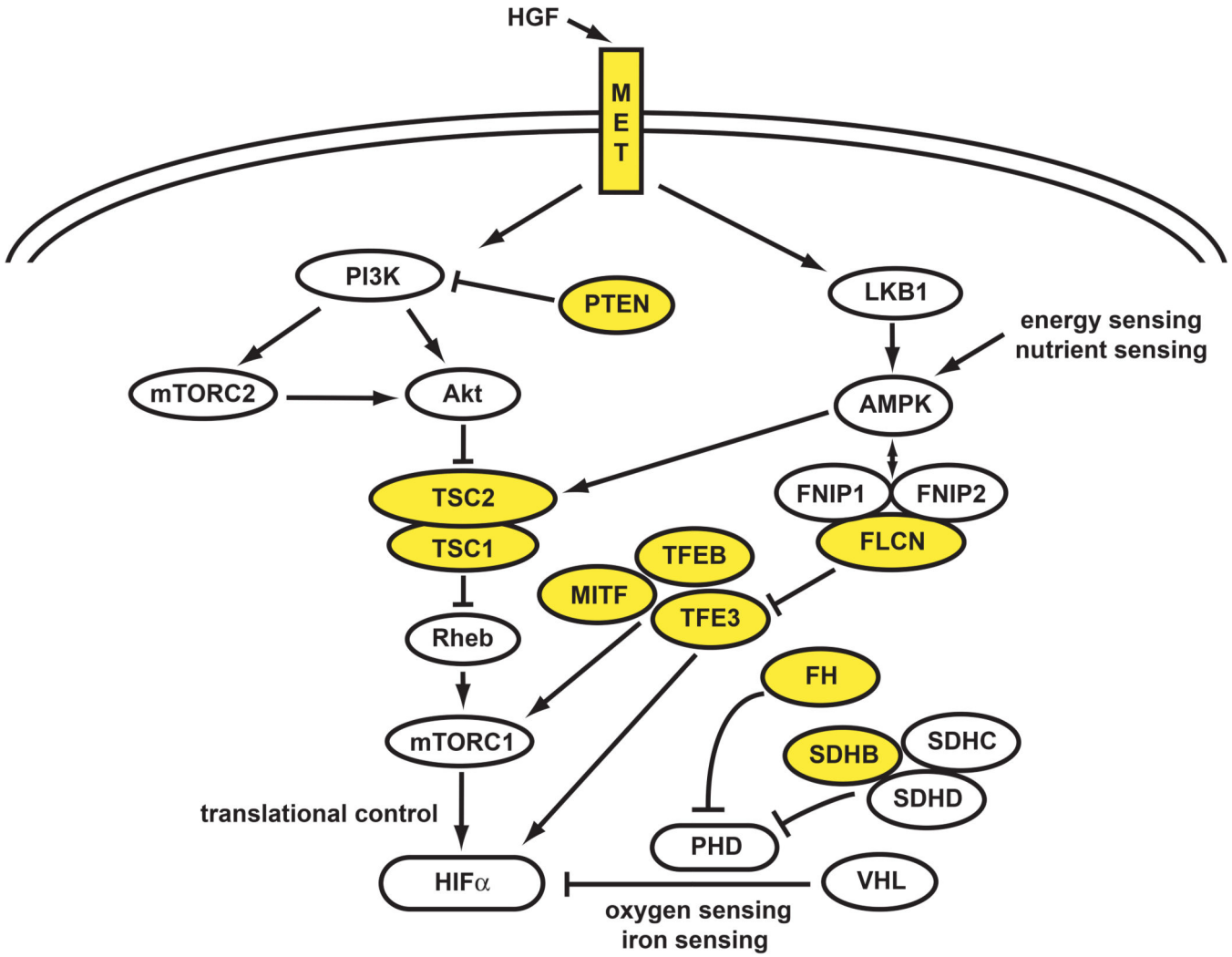

Figure 2. Non-Clear Cell Kidney Cancer Pathways

Non-clear cell kidney cancer is a metabolic disease. The genes that are associated with non-clear cell kidney cancer, MET, FLCN, fumarate hydratase, succinate dehydrogenase, TFE3, TFEB, MITF, TSC1, TSC2, and PTEN are all associated with abnormalities of the cell's ability to sense oxygen, iron, nutrients or energy. Adapted from Linehan, 2012 (88)