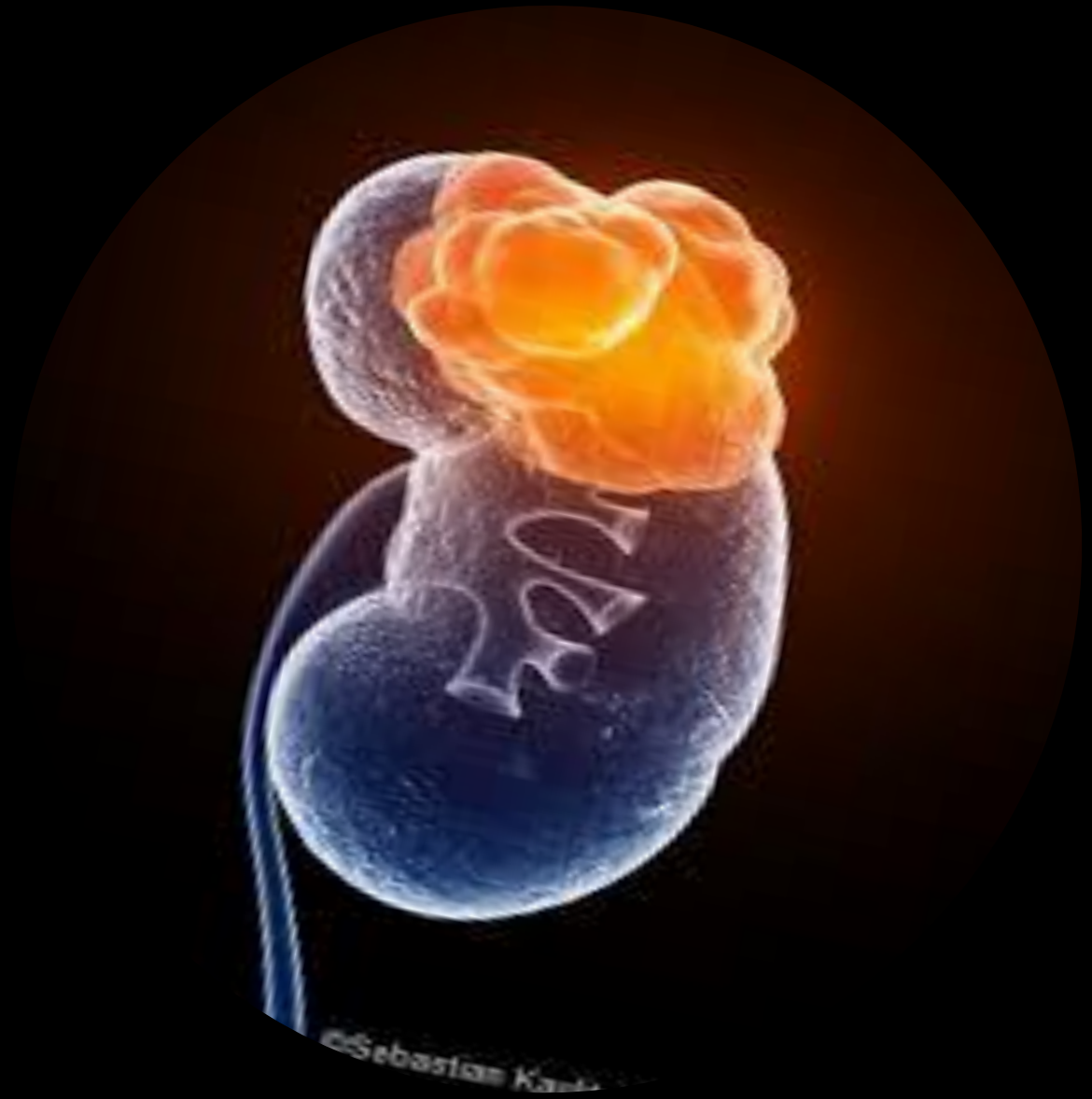


Renal cell carcinoma

Maya Kolin, MD

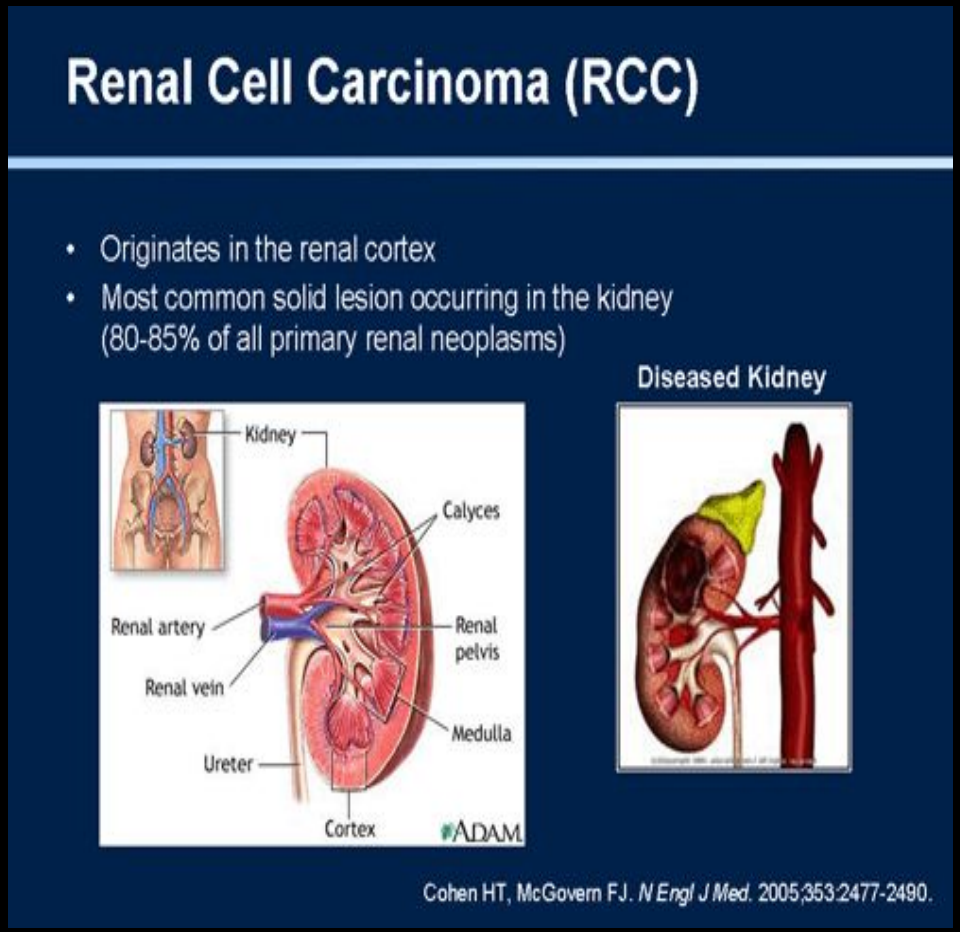
Of Oncology Department

Hillel Yaffe Medical Center

29.11.2021

Epidemiology

- Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80-85% of all primary renal neoplasms
- Transitional cell carcinomas of the renal pelvis are the next most common (8 %)
- Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, occur infrequently
- Renal medullary carcinoma is a rare form of RCC, seen in sickle cell disease
- Nephroblastoma or Wilms tumor occur in children



Epidemiology

- Worldwide, in 2018, there were an estimated 403,000 new cases of RCC and 175,000 deaths due to kidney cancer
- The incidence of renal cell carcinoma (RCC) varies widely from region to region, with the highest rates observed in the Czech Republic and North America
- In the United States, there are approximately 76,000 new cases and almost 14,000 deaths from RCC each year

Epidemiology

- RCC is approximately twofold more common in men compared with women
- RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age
- It is unusual in patients under 40 years of age and rare in children

Some notable features of RCC include:

- Common diagnosis of asymptomatic disease
- Resistance to cytotoxic agents
- Relative resistance to radiotherapy
- Variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression

Survival

- The incidence of RCC has risen threefold higher than the mortality rate
- The five-year survival rate of patients with kidney cancer has doubled over the last 60 years, from 34% in 1954 to 62% in 1996 and 75% from 2009 to 2015
- This improved survival is mostly due to earlier detection of these tumors at smaller sizes (ie, <4 cm) and curative surgical treatment

Risk factors associated with a increased incidence of RCC

- Smoking
- Hypertension
- Obesity….

Otherwise, for patients with newly diagnosed RCC, excess body weight is associated with a lower stage and lower grade disease

- Furthermore, in patients with metastatic disease, RCC is associated with a longer overall survival for those with excess body weight compared with those with normal or below normal body weight

- The improved prognosis in these patients may be associated with decreased expression of the fatty acid synthase (*FASN*) gene

Other risk factors associated with a increased incidence of RCC

- Acquired cystic disease of the kidney
- Chronic kidney disease, a decreasing estimated glomerular filtration rate (eGFR)
- The risk of developing RCC has been estimated to be up to 30 times greater in dialysis patients with acquired polycystic disease of the kidney than in the general population
- Among chronic dialysis patients, the incidence of acquired cystic disease is approximately 35-50%, and approximately 6% of these patients eventually develop RCC

Other risk factors associated with a increased incidence of RCC

- Occupational exposure to toxic compounds, such as cadmium, asbestos, and petroleum byproducts

- Epidemiologic studies have demonstrated an increased risk for RCC with heavy use of aspirin, nonsteroidal anti inflammatory drugs (NSAIDS), and acetaminophen, although the risk may vary depending on the agent

- The prolonged ingestion of analgesic combinations, particularly compounds containing phenacetin (of which acetaminophen is a major metabolite) and aspirin, can lead to chronic renal failure. Such patients are at increased risk for urothelial tumors

Other risk factors associated with a increased incidence of RCC

- Cytotoxic chemotherapy — The use of cytotoxic chemotherapy in childhood for malignancies, autoimmune disorders, or bone marrow transplant conditioning has been associated with the subsequent development of translocation RCC

- Chronic hepatitis C infection

- Sickle cell disease — Patients with sickle cell trait and (to a lesser extent) sickle cell disease are at risk for renal medullary carcinoma

Other risk factors associated with a increased incidence of RCC

- Kidney stones---A history of kidney stones may be associated with both RCC and transitional cell carcinoma of the upper urinary tract

- In a meta-analysis that pooled data from almost 63,000 patients with kidney stones, the risk ratio of developing RCC was 1.96 (95% CI 1.24-2.49), and the increased risk appeared to be largely limited to men. The risk ratio for transitional cell carcinoma was 2.14

Risk factors for RCC

- The risk of a second, metachronous RCC is increased in patients who have been treated for one renal cancer

- This increased risk is most pronounced with younger age at the first RCC, suggesting that early onset renal cancer has a genetic component

Other factors that modify risk

- Diabetes mellitus
- Polycystic kidney disease
- Alcohol (protective effect)?
- Childhood cancer survivors — At least one study suggests that childhood cancer survivors are at an increased risk for RCC, particularly if they were previously treated with radiotherapy directed at the kidney or with cisplatin
-

Genetic factors

- Although most RCCs are sporadic, several syndromes associated with RCC have been described

- Factors that favor a hereditary contribution in patients without a clear genetic disease include:

- first degree relatives with a tumor
- onset before the age of 40
- bilateral or multifocal disease

- Patients with inherited polycystic disease may have an increased risk of RCC (as well as liver and colon cancer), even in the absence of chronic kidney disease

Clinical and molecular characteristics of the most common hereditary kidney cancer syndromes

Syndrome	Gene/protein	Chromosomal locus	Potential pathway	Clinical features
Hereditary papillary renal cancer	c-MET	7q31	HGFR	Papillary type I renal cell carcinoma
Hereditary leiomyomatosis renal cell carcinoma	Fumarate hydratase	1q42	Krebs cycle/HIF1	Papillary type II renal cell carcinoma/skin carcinoma, and uterine leiomyoma
Birt-Hogg-Dube	Folliculin	17p11	mTOR	Chromophobe, oncocytic, hybrid, and clear cell renal cell carcinoma, fibrofolliculoma, pulmonary cysts, pneumothorax
Hereditary paraganglioma and pheochromocytoma	Succinate dehydrogenase	5p15	Krebs cycle/hypoxia	Clear cell, chromophobe renal cell carcinoma, pheochromocytoma, paragangliomas
Tuberous sclerosis complex (TSC)	TSC1 TSC2	9q34 16p13	mTOR	Clear cell renal cell carcinoma, angiomyolipoma
von Hippel-Lindau (VHL)	VHL gene	3p25	HIF-1	Clear cell renal cell carcinoma, hemangioblastomas, retinal angiomas, pheochromocytomas, endolymphatic sac tumors of the middle ear

HGFR: hepatocyte growth factor receptor (also known as c-MET); HIF-1: hypoxia-inducible factor 1; mTOR: mammalian target of rapamycin.

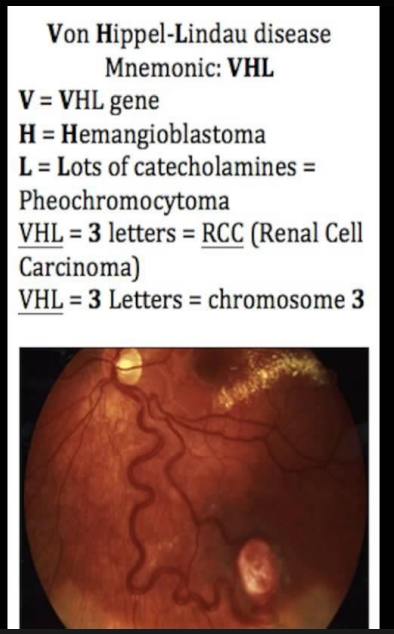
Hereditary cancer kidney syndromes

Von Hippel-Lindau (VHL) disease

- Von Hippel-Lindau (VHL) syndrome is characterized by germline mutation of VHL gene localized on chromosome 3p, development of clear cell RCC in approximately 35% of individuals

- Von Hippel-Lindau (VHL) syndrome is an autosomal dominant disorder

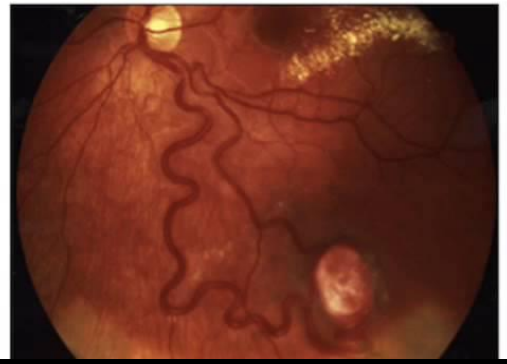
- A pathogenic variant in the VHL gene diagnostic for VHL disease is present in approximately 1 in 36,000 individuals



VHL-associated tumours

- Hemangioblastomas of CNS (cerebellum, brainstem, spinal cord)
- Retinal hemangioblastomas
- ccRCCs
- Pheochromocytomas
- Endolymphatic sac tumours of the middle ear
- Serous cystadenomas and neuroendocrine tumors of pancreas

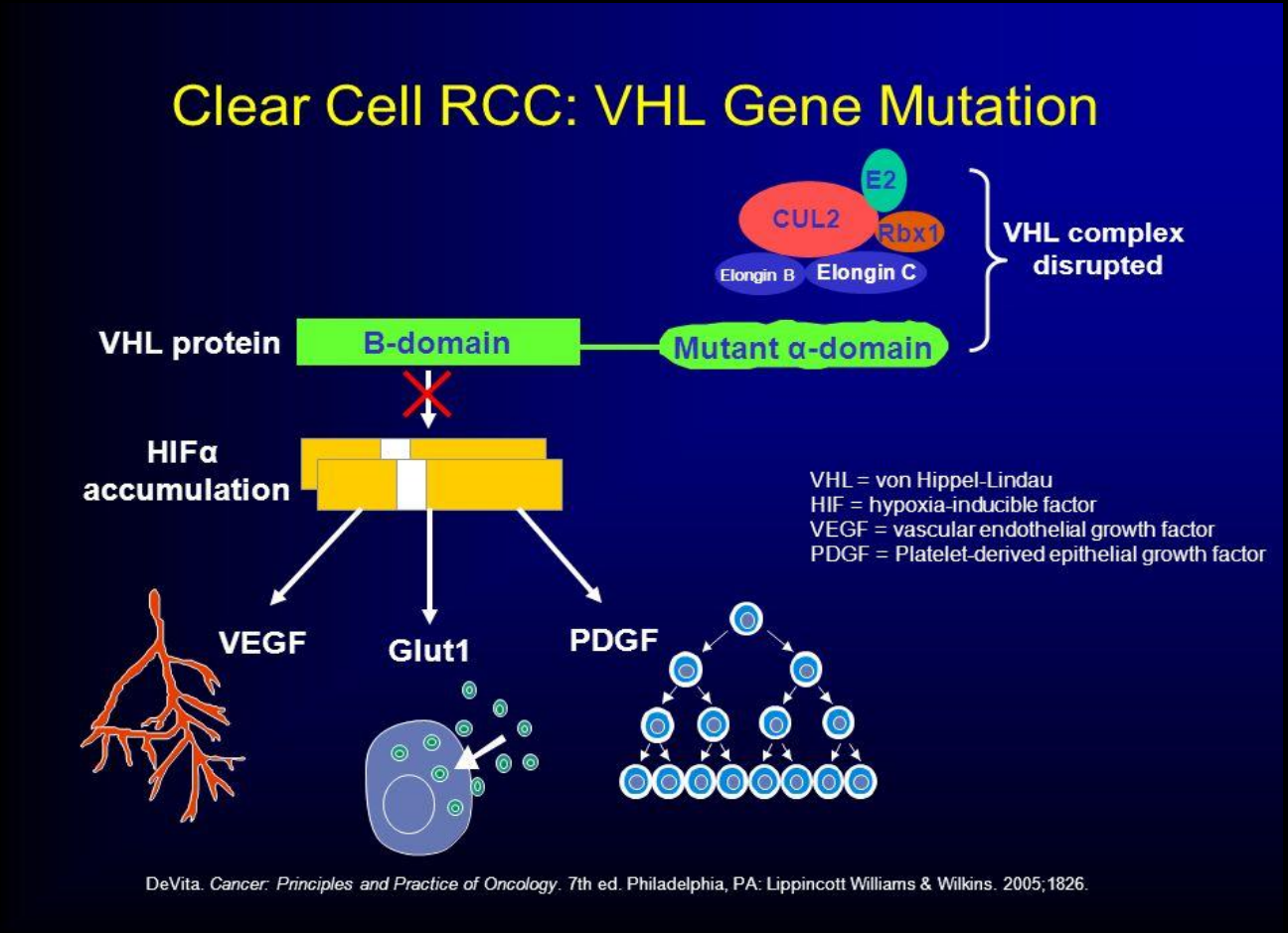
Von Hippel-Lindau disease
Mnemonic: **VHL**
V = **V**HL gene
H = **H**emangioblastoma
L = **L**ots of catecholamines = Pheochromocytoma
VHL = **3** letters = RCC (Renal Cell Carcinoma)
VHL = **3** Letters = chromosome **3**



The pathogenesis of VHL disease has been linked to mutations in the VHL gene

VHL protein, the product of the VHL gene, is a tumor suppressor protein that performs a number of important cellular functions

- Mutation in the VHL gene causes accumulation of HIF1A and HIF2A factors (substrates for the product of the VHL gene) and increased levels of erythropoietin, vascular endothelial growth factor (VEGF), and other growth factors, providing a stimulus for tumor growth



Hereditary cancer kidney syndromes

- **Hereditary papillary renal carcinoma (HPRC)** is a familial cancer syndrome in which affected individuals are at risk for the development of type 1 papillary renal cell carcinomas

- **Hereditary leiomyomatosis and renal cell cancer (HLRCC)** is a syndrome in which affected family members have cutaneous and uterine leiomyomas, and/or papillary type 2 RCCs

Clinical and molecular characteristics of the most common hereditary kidney cancer syndromes

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Hereditary cancer kidney syndromes

- **Birt-Hogg-Dubé syndrome** is a rare human autosomal dominant genetic disorder characterized by fibrofolliculomas (benign tumors arising in hair follicles), pulmonary cysts, pneumothorax, kidney tumors

- The renal tumors are usually of the chromophobe type, but they can exist as hybrids with other cell types (clear cell, oncocytic)

- This disorder is associated with mutations in the FLCN gene, which codes for folliculin

Clinical and molecular characteristics of the most common hereditary kidney cancer syndromes

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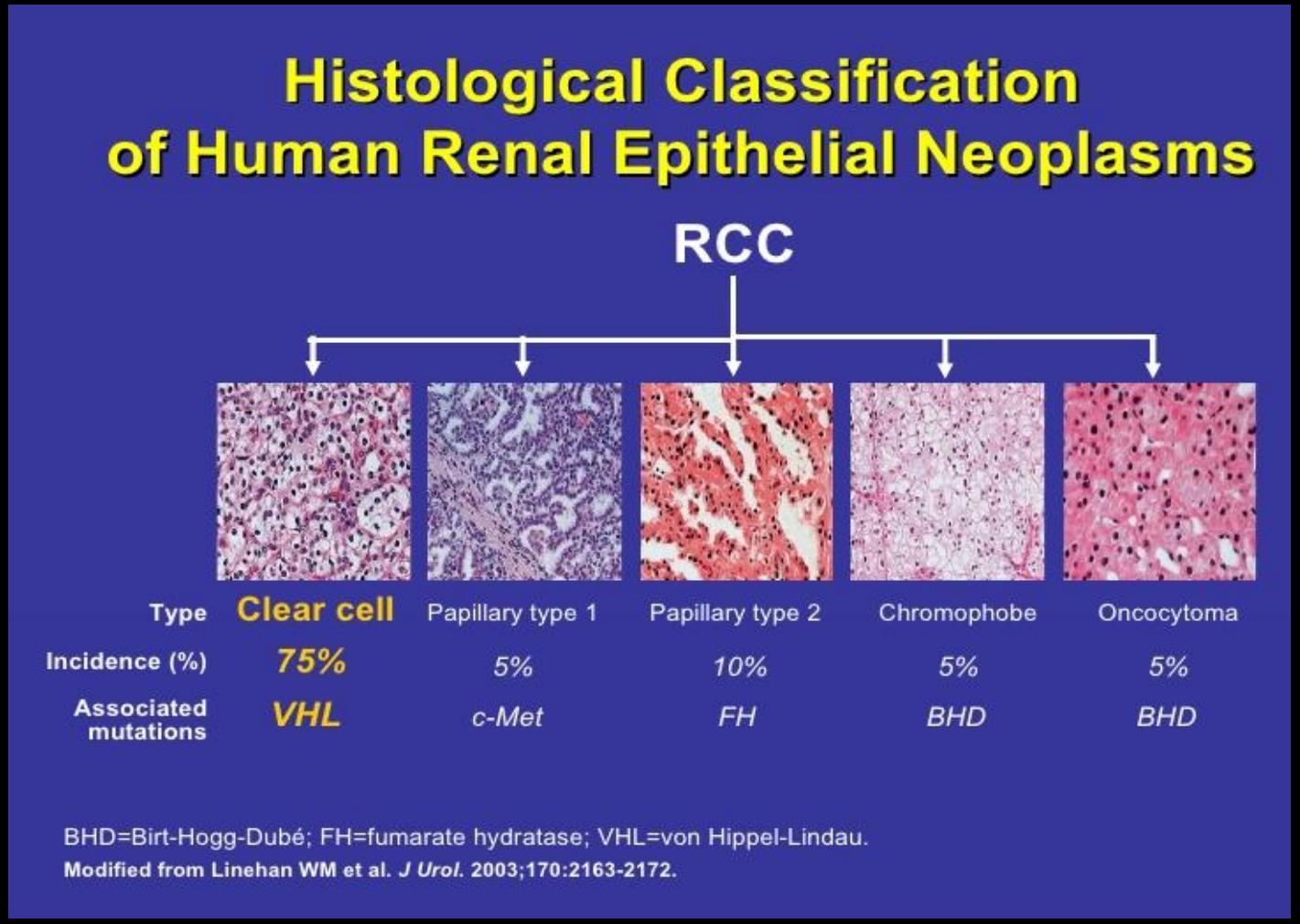
HGFR: hepatocyte growth factor receptor (also known as c-MET); HIF-1: hypoxia-inducible factor 1; mTOR: mammalian target of rapamycin.

Histological classification of RCC

- Clear cell carcinoma (70% of cases)
- Papillary tumors (10%)
- Chromophobe tumors (≤5%)
- Oncocytomas (5–10%)
- Collecting duct or Bellini duct tumors (<1%)
- Translocation carcinoma (<1%)



Pathology RCC

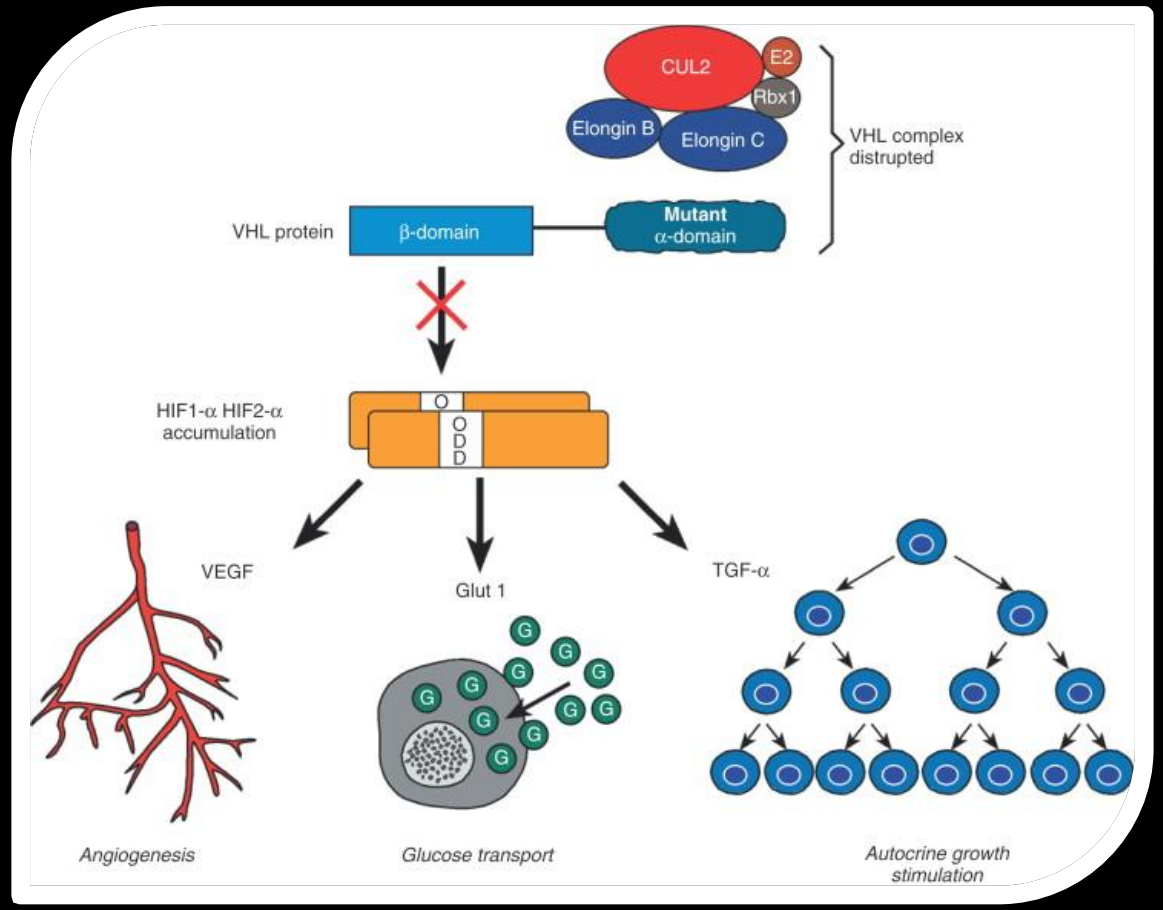
- **Papillary tumors** tend to be bilateral and multifocal
- **Chromophobe tumors** have a more indolent clinical course
- **Oncocytomas** are considered benign neoplasms
- **Collecting duct carcinomas**, which are thought to arise from the collecting ducts within the renal medulla, are rare but often very aggressive
- **Medullary carcinoma** has histopathologic and clinical features similar to those of collecting duct carcinoma, associated with sickle cell trait

Clear cell RCC

- **Clear cell tumors**, the predominant histology, are found in >80% of patients who develop metastases

- Clear cell tumors arise from the epithelial cells of the proximal tubules and usually show chromosome 3p deletions

- Deletions of 3p21–26 (where the VHL gene maps) are identified in patients with familial as well as sporadic tumors

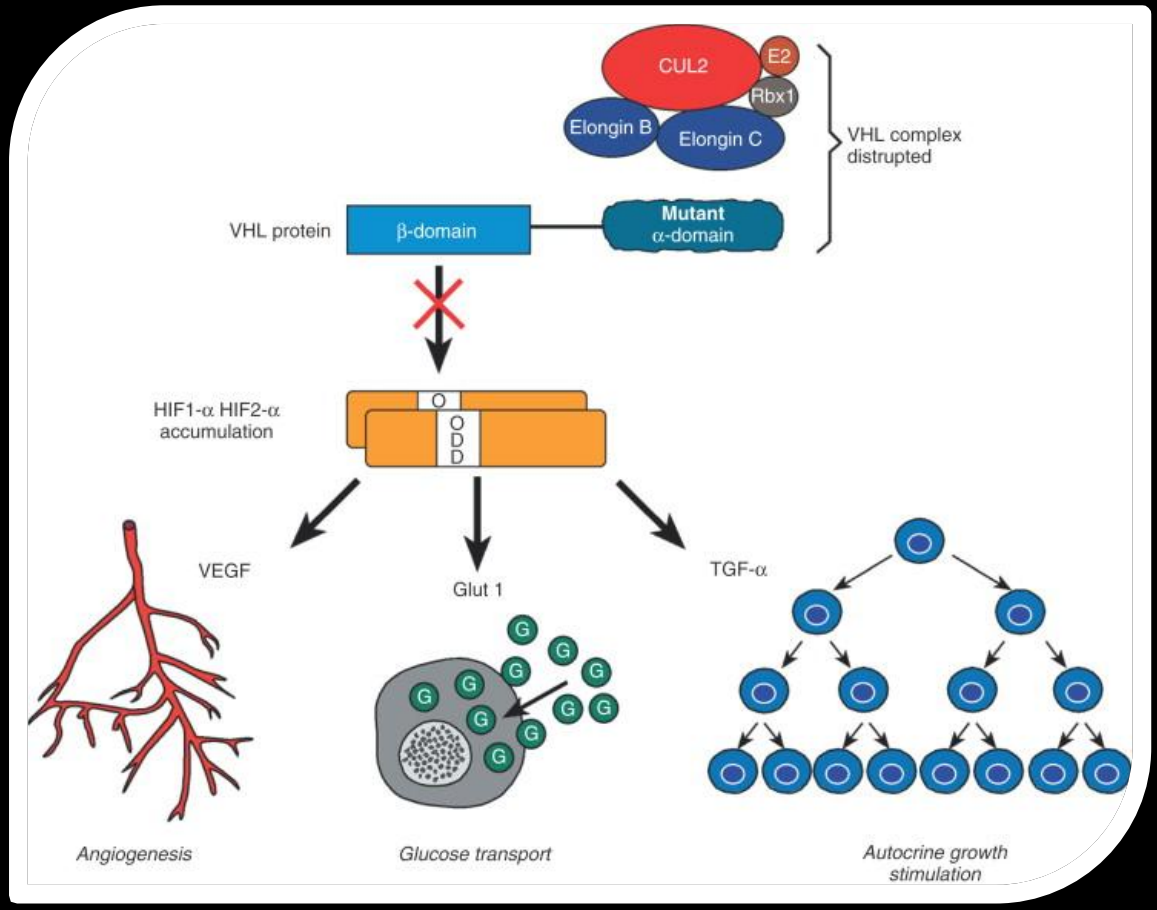


Clear cell RCC

VHL is the gene most frequently mutated in clear cell RCC

- **VHL gene encodes a tumor suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins**

- **Inactivation of VHL leads to overexpression of these agonists of the VEGF and PDGF receptors, which promote tumor angiogenesis and tumor growth**



Important!

- Although these tumors have a clear clonal origin and often contain VHL mutations in common, different portions of the primary tumor and different metastatic sites may have wide variation in genetic lesions

- This tumor heterogeneity may underlie the emergence of treatment resistance

While VHL is the gene most frequently mutated in clear cell RCC (52% of cases), other genes are implicated as well

- PBRM1 in 40% of cases

  SETD2 in 15% of cases

  BAP1 in 15% of cases

- These three genes, all part of the chromatin remodeling/histone methylation pathway, are also located on the short arm of chromosome 3p

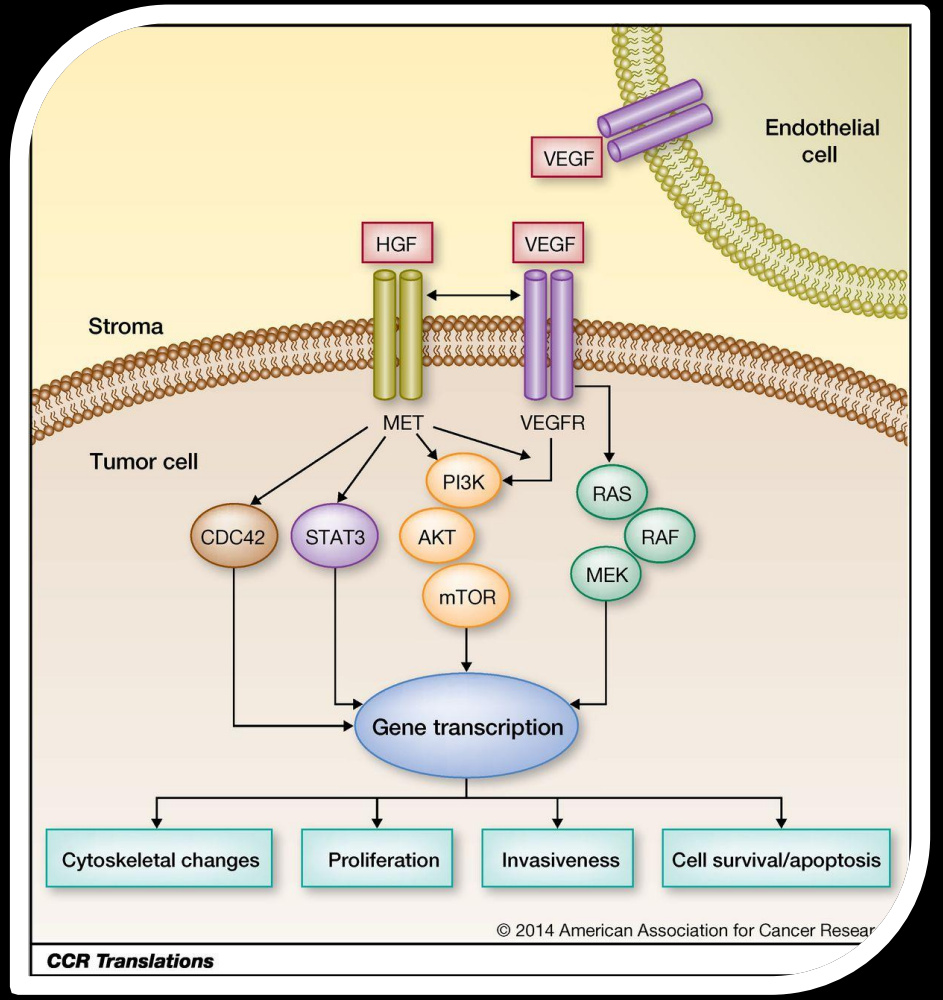
- Mutations in BAP1 have been linked to shorter survival in renal cancer

- In a subset of clear cell RCCs, alterations have been found in components of the mammalian target of rapamycin (mTOR) pathway, spurring the study of mTOR inhibitors in renal cancer

Papillary RCC type 1

Approximately 10% of RCC are of the papillary subtype

- **Type 1 papillary RCC tumors are associated with MET pathway dysregulation, and patients can present with indolent disease and have a more favorable prognosis**



c-MET is a receptor tyrosine kinase that, after binding with its ligand, hepatocyte growth factor, activates a wide range of different cellular signaling pathways, including those involved in proliferation, motility, migration and invasion

Papillary RCC type 2

- Type 2 papillary RCC tumors may be characterized by sporadic gene mutations (such as those involving 1p-, 3p-, or +5q) or germline mutations in the fumarate hydratase gene, which is associated with hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. These patients typically present with more aggressive disease and have a less favorable prognosis

Clinical presentation of RCC

- Hematuria
- Flank or abdominal pain
- Fever
- Weight loss
- Anemia
- Varicocele

Symptoms[1-3]

- Many patients with RCC are asymptomatic and have nonpalpable renal masses until late in the natural disease course
- Common local symptoms
  - Hematuria
  - Ipsilateral flank or abdominal pain
  - Palpable mass
- Common systemic symptoms
  - Paraneoplastic disorders (eg, hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anemia, abnormal liver function, hypercalcemia, polycythemia, etc.)
  - Pain or mass related to metastatic disease

1. Lee CT, et al. *Urol Oncol*. 2002;7:135-140.
2. Patard JJ, et al. *Eur Urol*. 2003;44:226-232.
3. Ljundberg B, et al. *Eur Urol*. 2007;51:1502-1510.

Physical exam

- The classic triad of RCC (flank pain, hematuria, and a palpable abdominal renal mass) occurs in at most 9% of patients; when present, it strongly suggests locally advanced disease

- An abdominal or flank mass (associated with lower pole tumors).

The mass is generally firm, homogeneous, nontender, and moves with respiration

Physical exam

- **Scrotal varicocele**, usually left sided, is observed in as many as 11 % of men with RCC. Varicocele typically fail to empty when the patient is recumbent. This finding should always arouse suspicion for a kidney tumor that has obstructed the gonadal vein where it enters the renal vein

- **Inferior vena cava involvement** can produce lower extremity edema, ascites, hepatic dysfunction and pulmonary emboli

Kidney cancer was called the “internist’s tumor” since it was often discovered from the initial presentation of a paraneoplastic syndrome

- Hypercalcemia
- Non metastatic hepatic dysfunction (Stauffer’s syndrome)
- Acquired dysfibrinogenemia
- Erythrocytosis (is noted at presentation in only ~3% of patients)
- Anemia, a sign of metastatic disease, is more common

At present time RCC most commonly detected as an incidental finding on a radiologic imaging

- Widespread use of radiologic cross-sectional imaging procedures (computed tomography [CT], ultrasound, magnetic resonance imaging [MRI]) contributes to earlier detection of renal mass

- The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with RCC and increased use of nephron-sparing surgery (partial nephrectomy)

The standard evaluation of patients with renal mass

- CT scan of the abdomen and pelvis
- Chest radiograph
- Urine analysis
- Urine cytology
- CT chest, If metastatic disease is suspected from the chest radiograph
- MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus, or when intravenous contrast administration given with CT is prohibited by impaired renal function

Differential diagnosis of renal mass

- Any solid renal masses should be suspected malignant until proven otherwise

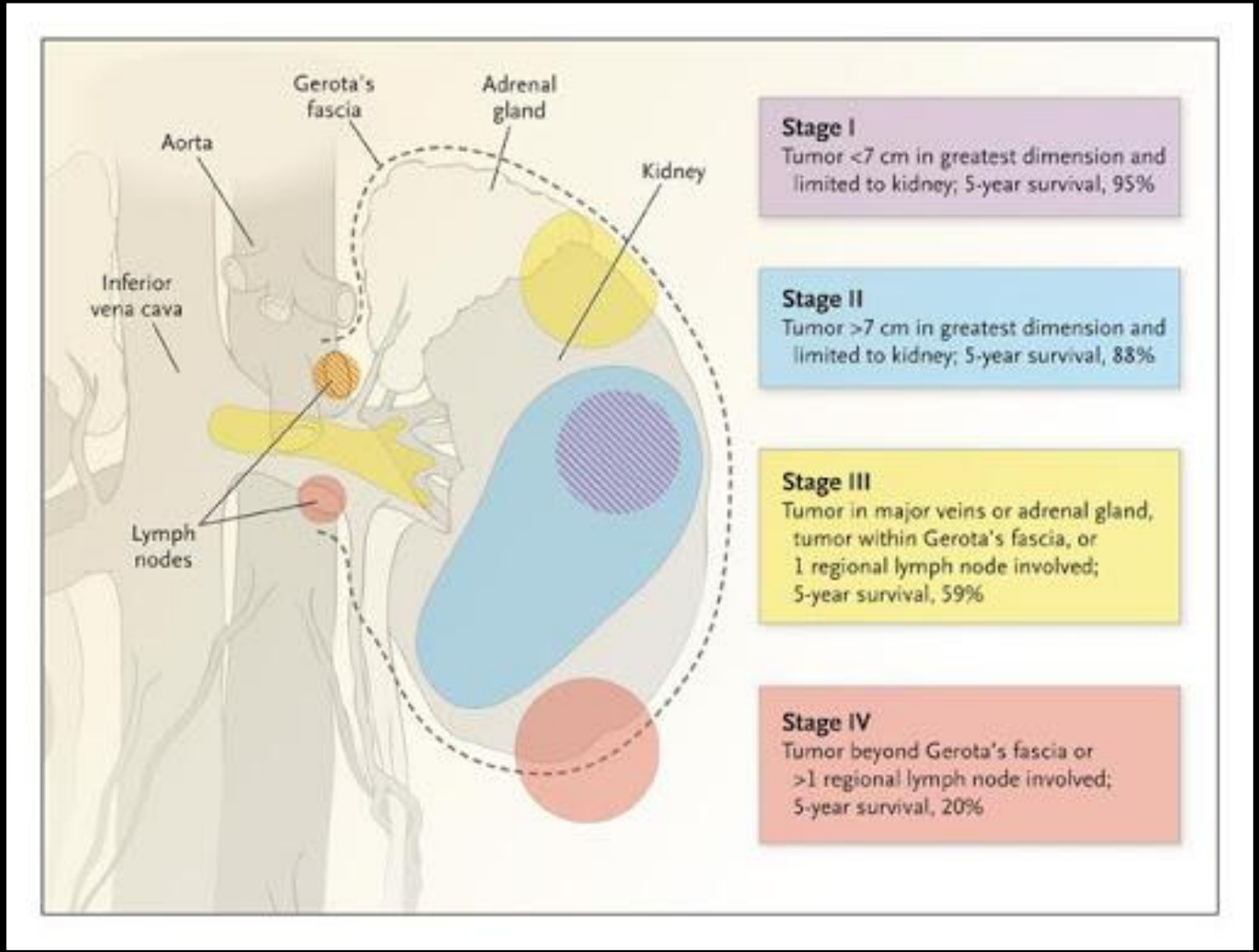
- The differential diagnosis of a renal mass includes RCC, cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other primary or metastatic cancers

- Less common malignancies that may involve the kidney include transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor

Staging is based on the American Joint Committee on Cancer (AJCC) staging system

- Stage I tumors are ≤7 cm in greatest diameter and confined to the kidney

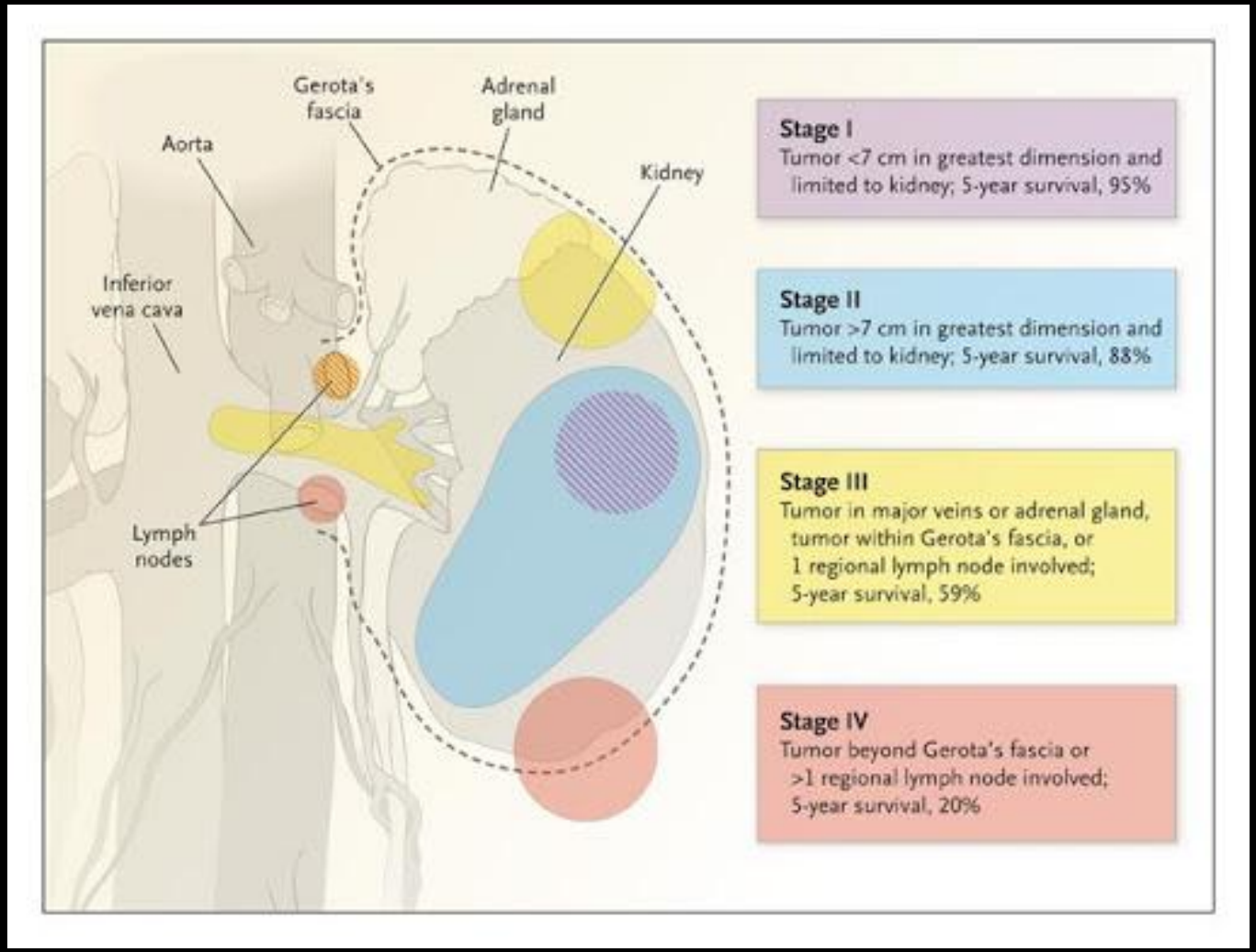
- Stage II tumors are >7 cm and confined to the kidney



Staging is based on the American Joint Committee on Cancer (AJCC) staging system

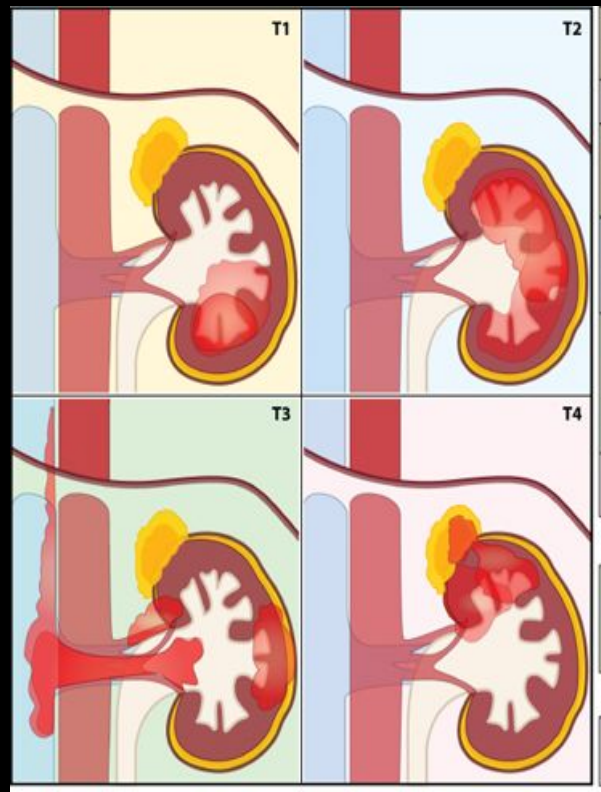
- Stage III tumors extend through the renal capsule but are confined to Gerota's fascia (IIIa), or involve a single hilar lymph node (N1)

- Stage IV disease includes tumors that have invaded adjacent organs or involve multiple lymph nodes or distant metastases



Staging and prognosis

- 65 % of patients present with stage I or II disease
- 15–20% with stage III
- 15–20% with stage IV



TNM	Involvement	Extent of Disease
T0	Primary not involved	
T1 T1a T1b	≤ 7 cm ≤ 4 cm ≥ 4 cm	limited to kidney
T2 T2a T2b	> 7 cm > 7 cm to ≤ 10 cm >10 cm	limited to kidney
T3 T3a T3b T3c	into major veins or perinephric tissues in renal vein or renal sinus fat into vena cava into vena cava	not beyond Gerota's fascia not beyond Gerota's fascia below diaphragm above diaphragm
T4	invasion beyond Gerota's fascia	including contiguous extensions & into ipsilateral adrenal gland

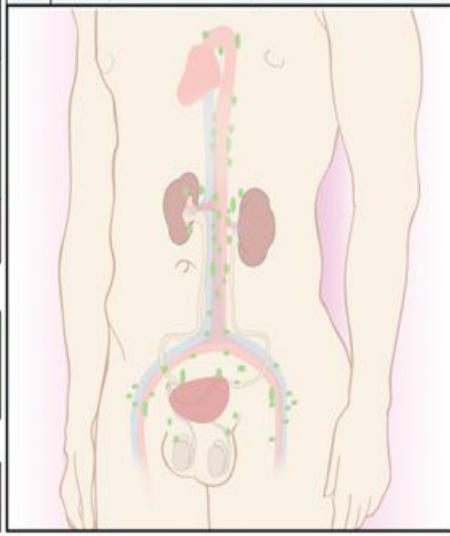
Regional

NX	Regional lymph nodes not assessed
N0	No lymph node involvment
N1	Regional lymph node involvment

Distant Metastases

M0	No distant metastases
M1	Distant metastases

Anatomic Stage / Prognostic Groups			
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2, T3	N1 N0 or N1	M0 M0
IV	T4 Any T	Any N Any N	M0 M1

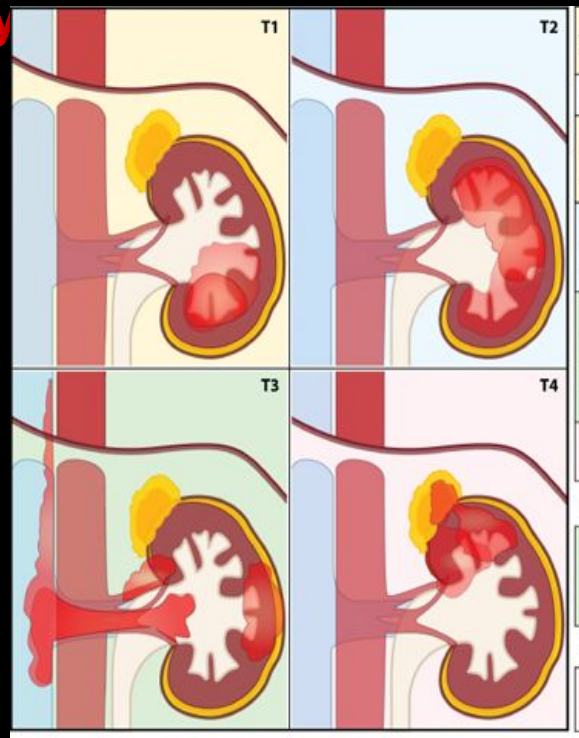


Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Staging and prognosis

The 5-year survival rate varies by stage

- 81% for stage I
- 74% for stage II
- 53% for stage III
- 8% for stage IV



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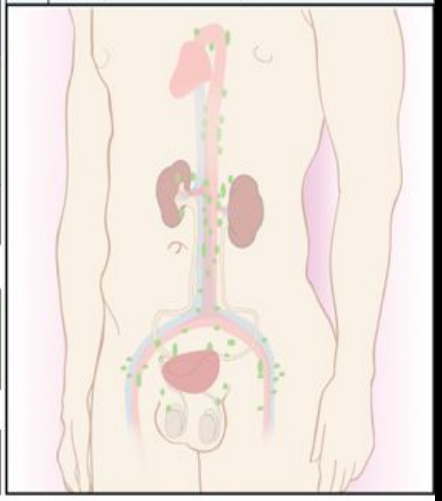
IV	T4 Any T	Any N Any N	M0 M1



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Prognostic risk models are helpful for counseling patients, and for anticipating survival rates when designing a clinical trial

- Prognostic model, developed by investigators at Memorial Sloan Kettering Cancer Center, incorporated five factors shown to correlate with worse survival in advanced renal cell carcinoma:

  - poor performance status
  - high serum lactate dehydrogenase
  - high serum calcium
  - low hemoglobin concentration
  - <1-year interval from diagnosis to treatment

Patients with zero risk factors had significantly longer median survival (30 months) than those with one or two risk factors (14 months) and those with three to five risk factors (5 months)

Prognostic risk models: IMDS

International Metastatic Renal Cell Carcinoma Database Consortium criteria

Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

Adapted from: Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013; 14:141.

Treatment of localized RCC

- The standard management for stage I or II tumors and selected cases of stage III disease is radical or partial nephrectomy

- A radical nephrectomy involves en bloc removal of Gerota's fascia and its contents, including the kidney, the ipsilateral adrenal gland in some cases, and adjacent hilar lymph nodes

- Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomy

Treatment of localized RCC

- Extension into the renal vein or inferior vena cava (stage III disease) does not preclude resection even if cardiopulmonary bypass is required

- If the tumor is resected, half of these patients have prolonged survival

Treatment of localized RCC

- Nephron-sparing approaches via open or laparoscopic surgery may be appropriate for patients who have impaired renal function or only one kidney, depending on the size and location of the lesion

- A nephron-sparing approach can also be used for patients with bilateral tumors

- Partial nephrectomy techniques are applied electively to resect small masses

Treatment of localized RCC

- Radical nephrectomy can lead to an increased risk for chronic kidney disease and is associated with increased risks of cardiovascular morbidity and mortality

- When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, and reduced frequency of late cardiovascular events

Adjuvant therapy

- Adjuvant therapy with interferon-α or radiation therapy following radical nephrectomy does not improve outcome, even in cases with a poor prognosis

- Adjuvant trials with sunitinib, an orally administered antiangiogenesis inhibitor, do not consistently show a benefit in prolonging time to relapse following nephrectomy

- Adjuvant therapy with pembrolizumab (monoclonal antibodiy directed against programmed cell death 1 protein PD-1) of patients at high risk of recurrent RCC following nephrectomy or following complete resection of primary and metastatic lesions extended disease free survival versus placebo

Treatment of metastatic RCC

- The most common sites of distant metastases are the lungs, lymph nodes, liver, bone, and brain

- These tumors may follow an unpredictable and protracted clinical course

Treatment of metastatic RCC

- Surgery has a limited role for patients with metastatic disease
- Long-term survival may occur in patients who relapse after nephrectomy in a solitary site that is removed
- Indications for nephrectomy with metastases at initial presentation are to alleviate pain or hemorrhage of a primary tumor

Treatment of metastatic RCC

- Radiation therapy is generally used for palliation of bone or brain metastases
- The types of radiotherapy most commonly used are external beam therapy and stereotactic radiotherapy
- In select cases, stereotactic ablative radiotherapy to a metastatic site may result in local control with relatively minimal toxicity

Treatment of metastatic RCC

- Metastatic renal cell carcinoma is refractory to cytotoxic chemotherapy

- The fields of immunology and oncology have been linked since the late 19th century, when the surgeon William Coley reported that injection of killed bacteria into sites of sarcoma could lead to tumor shrinkage

-

Treatment of metastatic RCC

- Removal of primary RCCs can evoke an immune response that occasionally results in spontaneous and dramatic remissions in metastases, particularly in the lungs

- These observations were followed by the clinical demonstration of antitumor activity with the cytokine interleukin 2 (IL-2) and interferon alfa (IFNa), although only a minority of patients derived major clinical benefit

- Cytokine therapy with IL-2 or interferon-α producd regression in 10–15% of patients

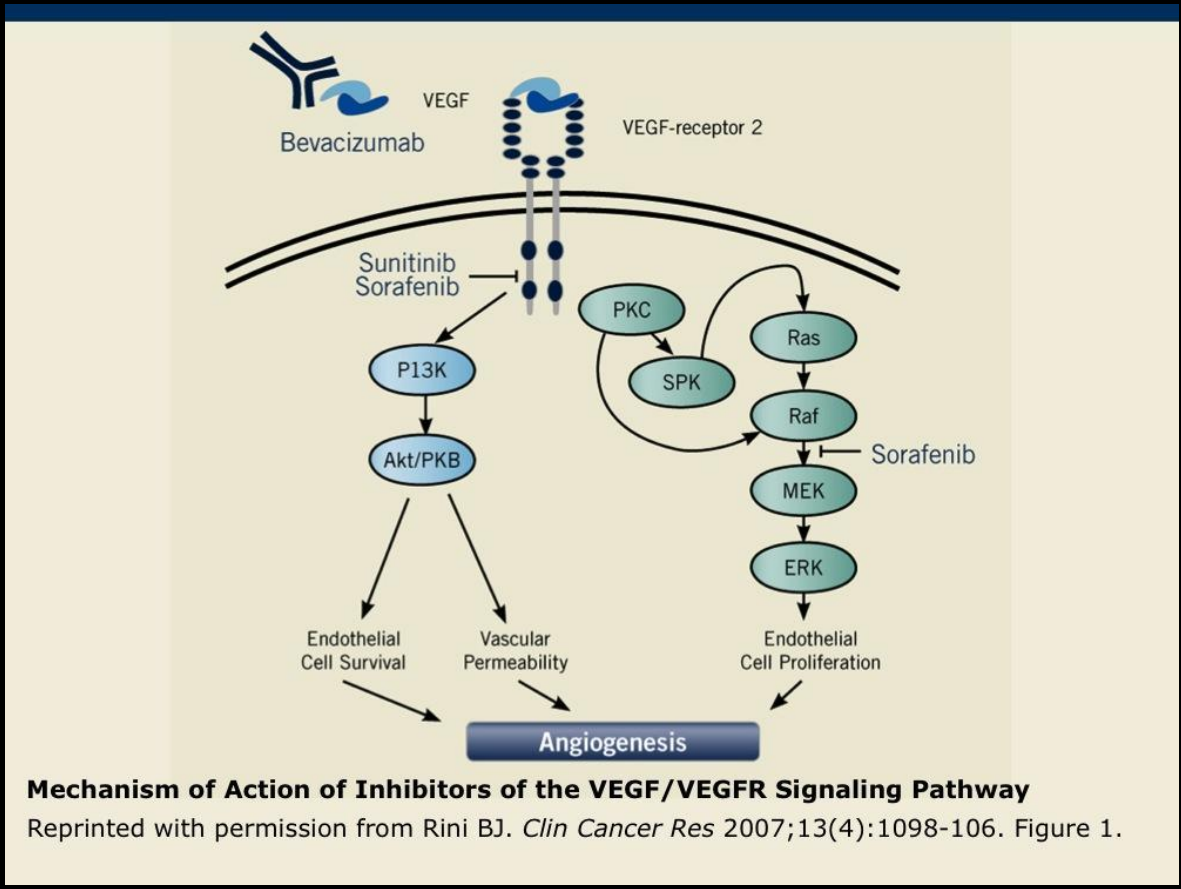
- IL-2 produced durable complete remission in a small proportion of cases with high levels of toxicity

Treatment of metastatic RCC

- The situation changed dramatically when two large-scale randomized trials established a role for antiangiogenic therapy

- These trials separately evaluated two orally administered antiangiogenic agents, sorafenib and sunitinb, that inhibited receptor tyrosine kinase signaling through the VEGF and PDGF receptors

- Both showed efficacy as second-line treatment following progression during or after cytokine treatment



Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway

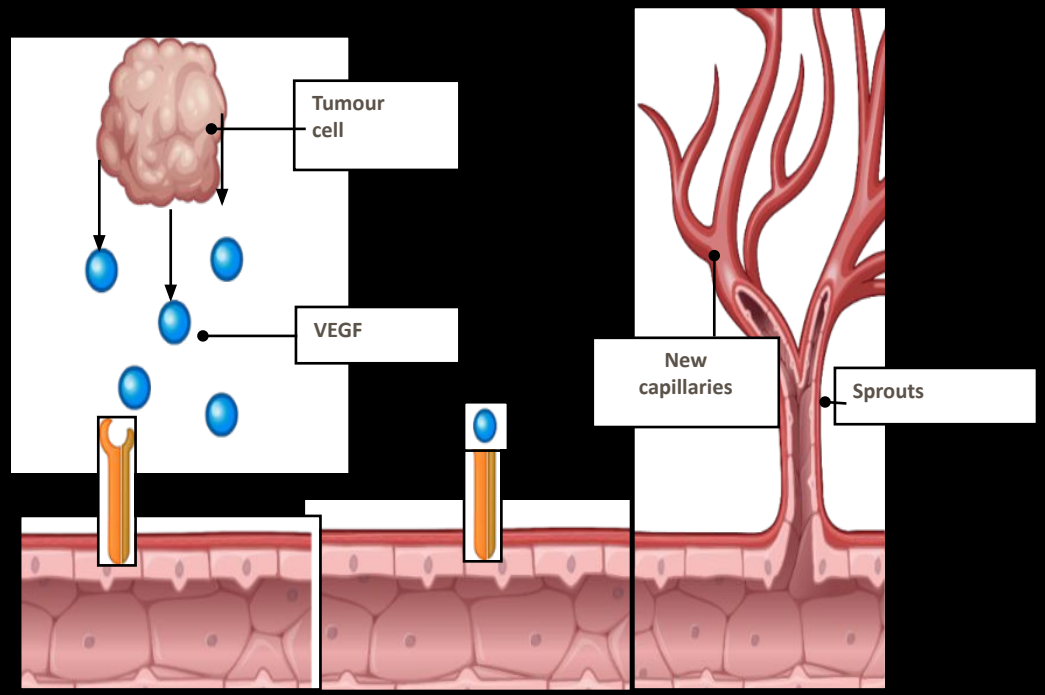
Reprinted with permission from Rini BJ. *Clin Cancer Res* 2007;13(4):1098-106. Figure 1.

The Role of VEGF in RCC

- Increased VEGF expression has been found in RCC and correlates with microvessel density, a measure of the extent of angiogenesis[1]

- After activation of HIF, VEGF is upregulated and binds to its receptor (VEGFR) on endothelial cell surfaces[2,3]
  - This promotes endothelial cell migration and proliferation – vital for the development of new tumour-induced blood vessels[1–3]

VEGF and VEGFR have proven to be attractive molecular targets for novel therapies for RCC because they play key roles in tumor angiogenesis



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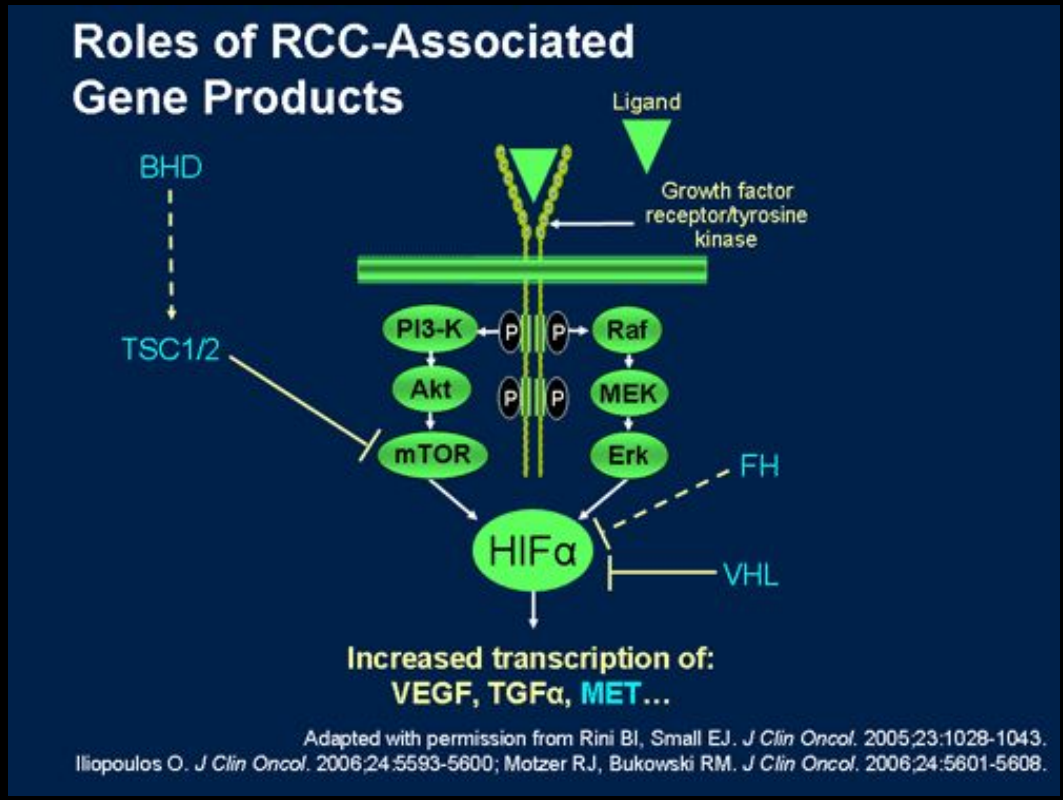
Drugs & Targets
-Multi-targeted TKIs-

Agent	Subtypes	Known targets
Sunitinib	DTC, MTC	VEGFR, PDGFR, c-kit, RET
Sorafenib	DTC, MTC	VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, C-Kit, RET, RAF and FGFR-1
Pazopanib	DTC	VEGFR, PDGFR, c-kit
Axitinib	DTC, MTC	VEGFR-1, 2, 3; PDGFR-α, β; KIT (but not RET)
Motesanib	DTC, MTC	VEGFR, PDGFR, c-kit, RET
Lenvatinib (E7080)	DTC	VEGFR-1, 2, 3, FGFR-1~4, RET, c-kit, PDGFR
Vandetanib (ZD6474)	MTC	RET, VEGFR2-3, EGFR
Cabozatinib (XL184)	MTC	MET, VEGFR2, and RET



Adapted with permission from Rini BI, Small EJ. *J Clin Oncol*. 2005;23:1028-1043. Iliopoulos O. *J Clin Oncol*. 2006;24:5593-5600; Motzer RJ, Bukowski RM. *J Clin Oncol*. 2006;24:5601-5608.

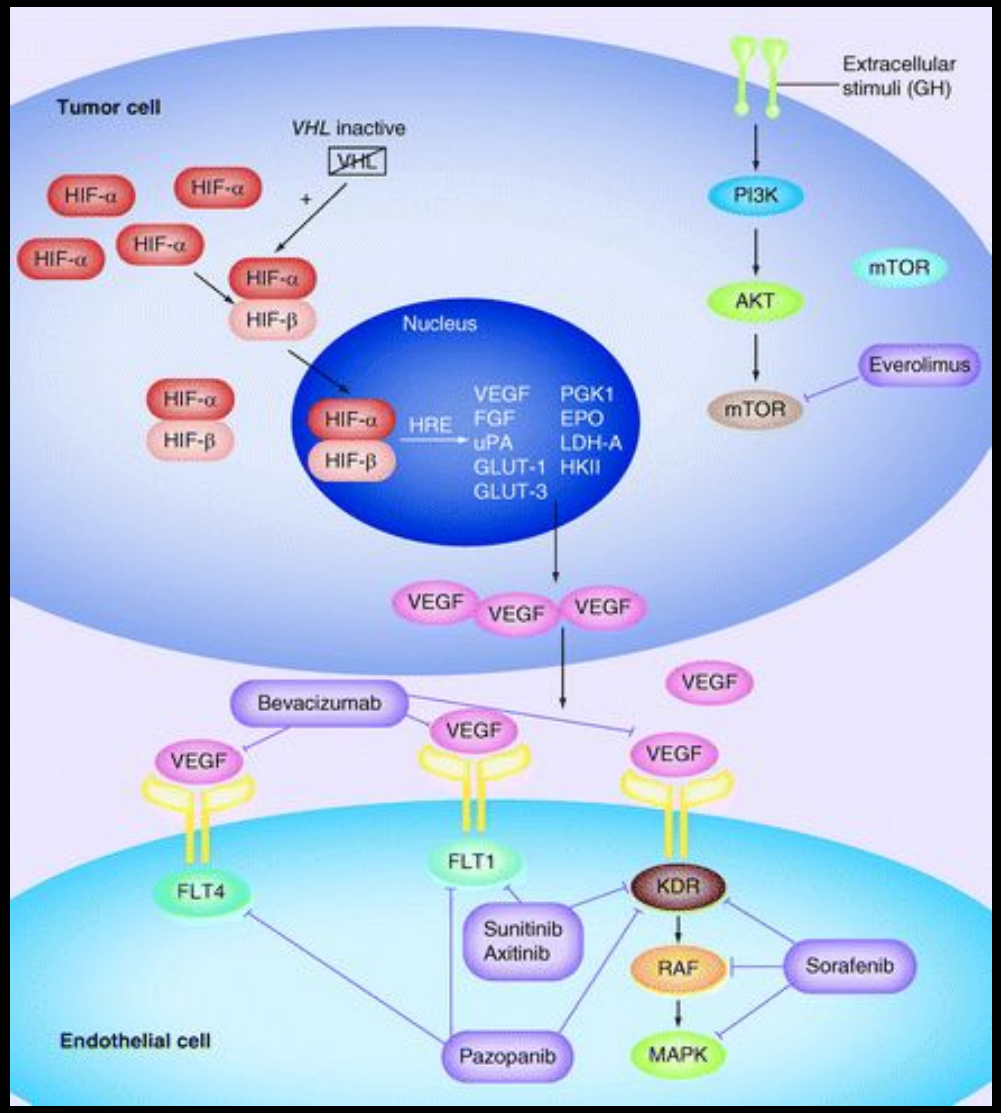
Treatment of metastatic RCC

- A randomized phase III trial comparing sunitinib to interferon-α showed superior efficacy for sunitinib with an acceptable safety profile

- This trial resulted in a change in the standard first-line treatment from interferon to sunitinib

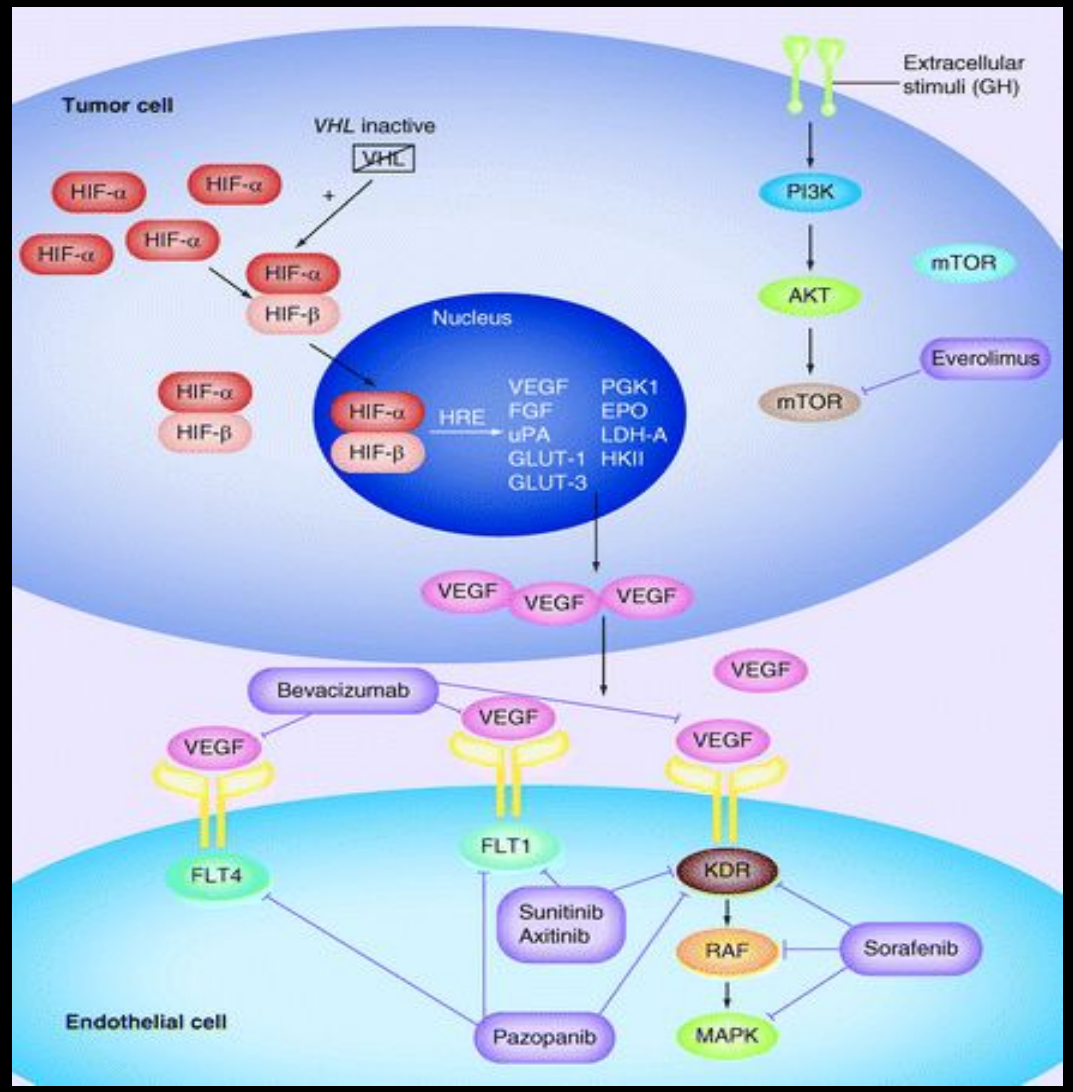
New systemic agents for metastatic renal cell carcinoma

- While the improvements in 5-year renal cancer survival rates over the past decades (50% in the mid-1970s, 57% in the late 1980s, and 74% for 2005–2012) can be attributed to widespread imaging leading to earlier discovery of tumors, the new agents are likely playing a an important role



New systemic agents for metastatic RCC

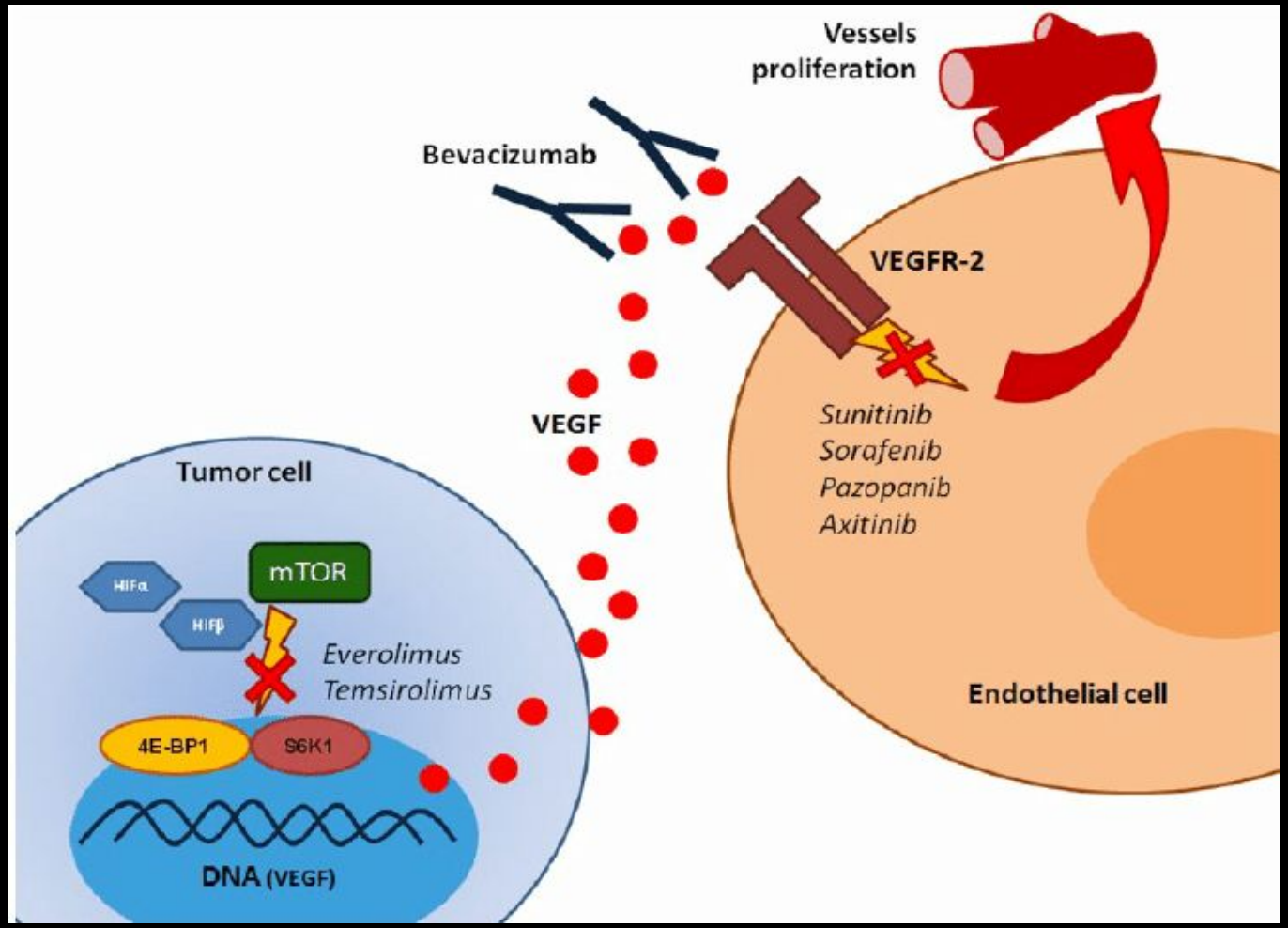
- **Pazopanib, axitinib, cabozantinib**, and **lenvatinib**, also tyrosine kinase inhibitors; the antiangiogenic **bevacizumab** (bevacizumab is a recombinant, humanized monoclonal antibody which binds to vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR; VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels), **mTOR inhibitors temsirolimus and everolimus**; **nivolumab** that inhibits PD-1…



Treatment of metastatic RCC

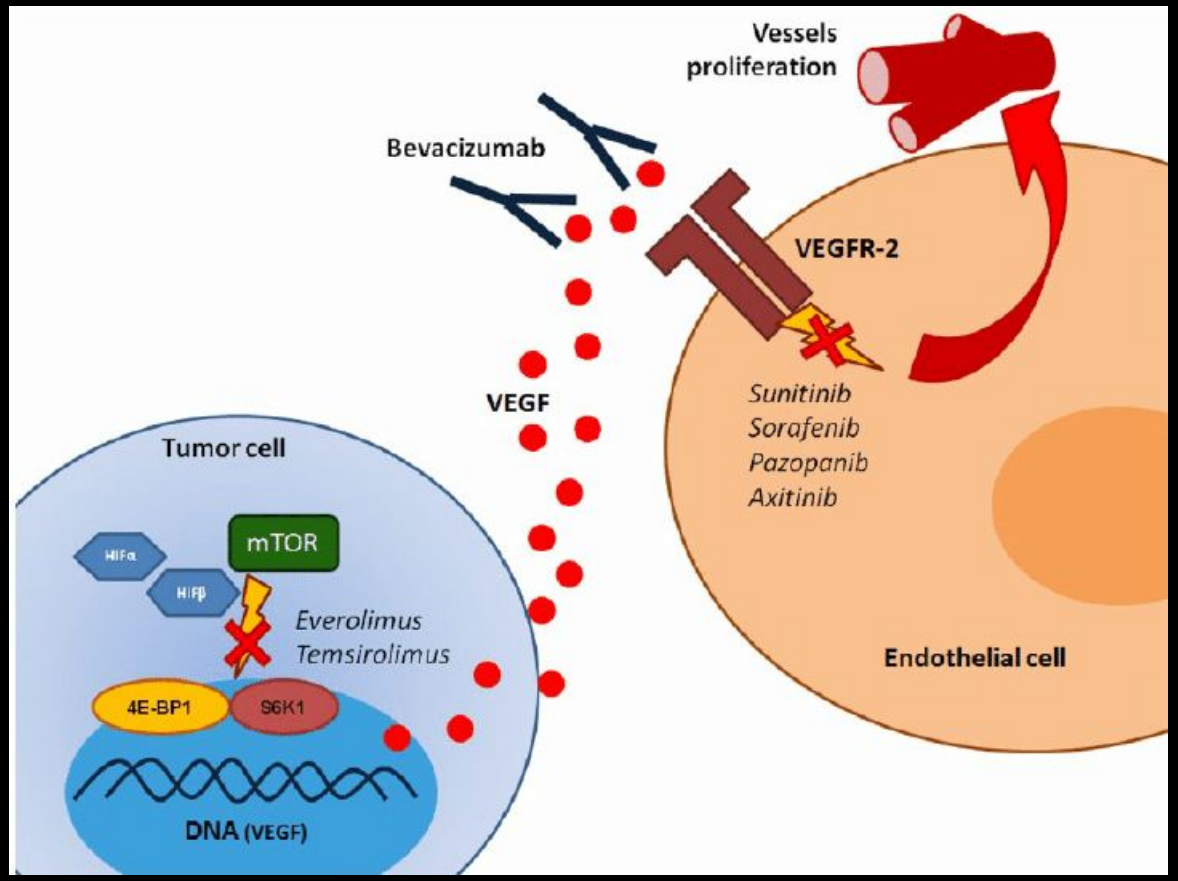
- Pazopanib was compared to sunitinib in a randomized first-line phase III trial

- Efficacy was similar, and there was less fatigue and skin toxicity, resulting in better quality-of-life scores for pazopanib compared with sunitinib, but different profile of adverse effects, liver toxicity more frequent



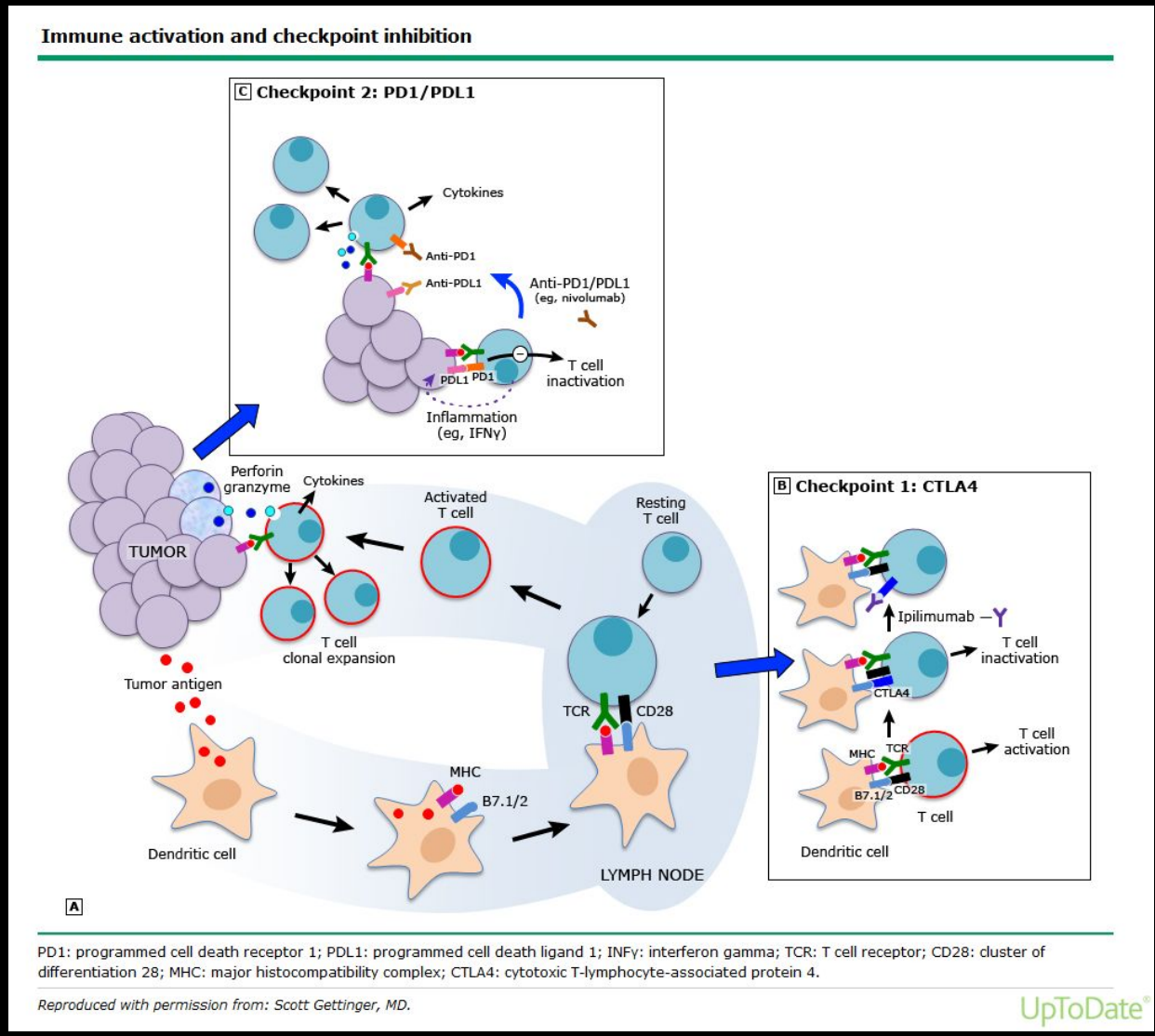
Treatment of metastatic RCC

- Temsirolimus showed activity in patients with untreated poor-prognosis tumors
- Nivolumab, cabozantinib, and lenvatinib plus everolimus were compared to everolimus in randomized trials and showed that patients lived longer with each of these agents compared to patients treated with everolimus
- Patients may benefit from the sequential use of agents following progression on first line therapy



Immunotherapy with checkpoint inhibitors has become a major modality for the treatment of metastatic RCC

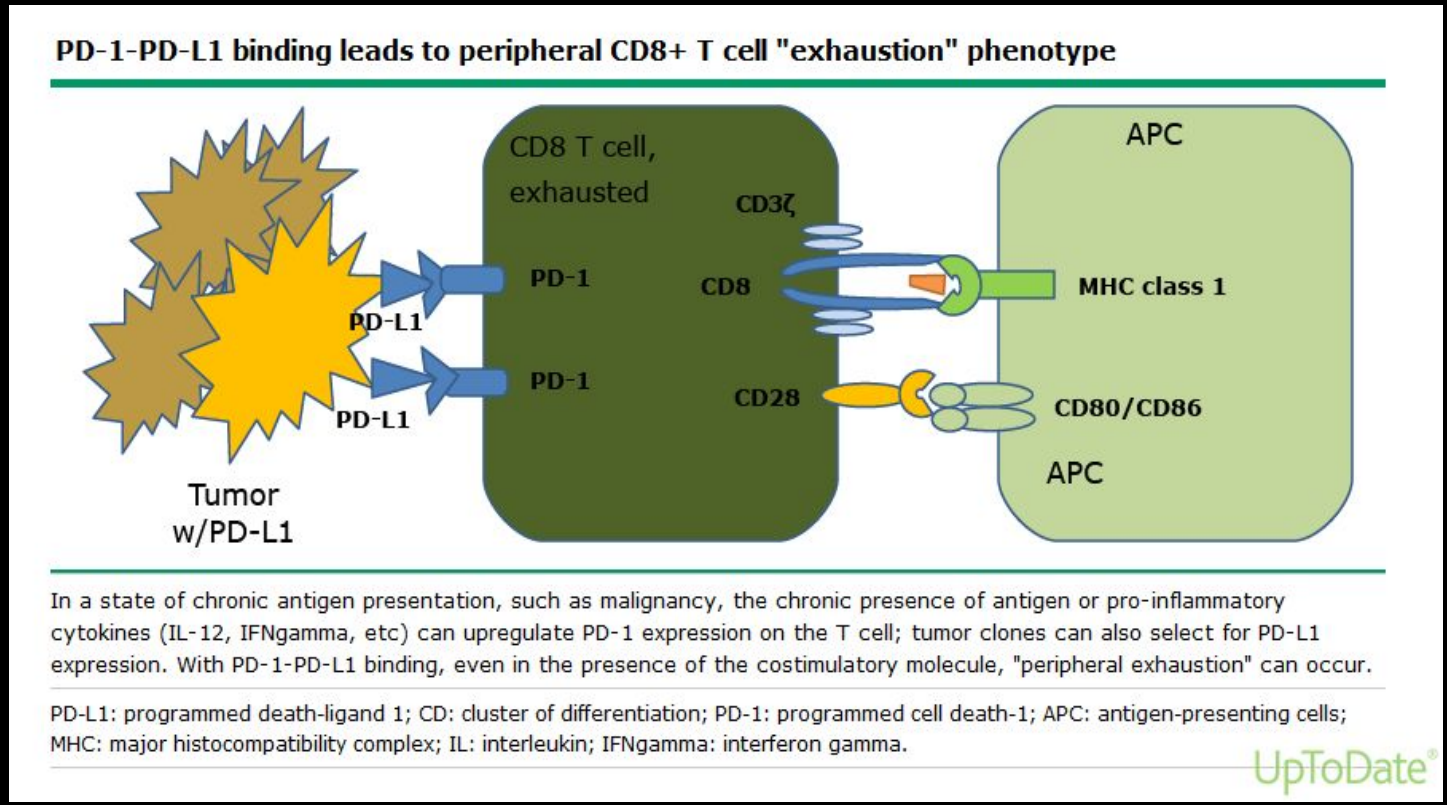
- Monoclonal antibodies directed against programmed cell death 1 protein PD-1 (nivolumab, pembrolizumab)
- Monoclonal antibodies that binds to programmed death ligand 1 (PD-L1) (avelumab)
- Anti cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab)



PD-1 and PDL-1

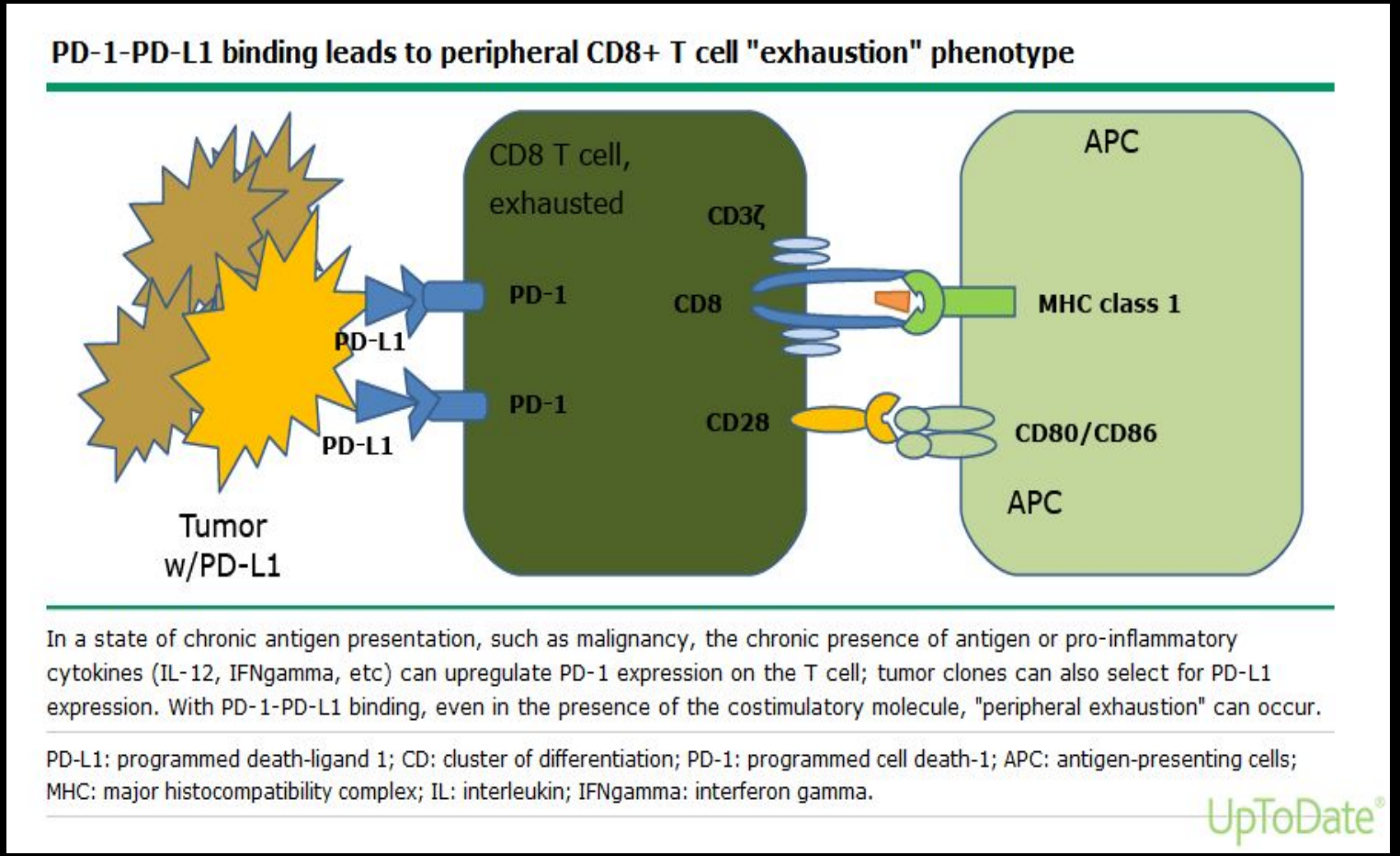
- **Programmed cell death 1 (PD-1)** is a transmembrane protein expressed on T cells, B cells, and NK cells
- **Programmed cell death 1 (PD-1)** is an inhibitory molecule that binds to the PD-1 ligand (PD-L1) and PD-L2

- **PD-L1** is expressed on the surface of multiple tissue types, including many tumor cells, as well as hematopoietic cells; PD-L2 is more restricted to hematopoietic cells



Additional cells such as NK cells, monocytes, and dendritic cells also express PD-1 and/or PD-L1

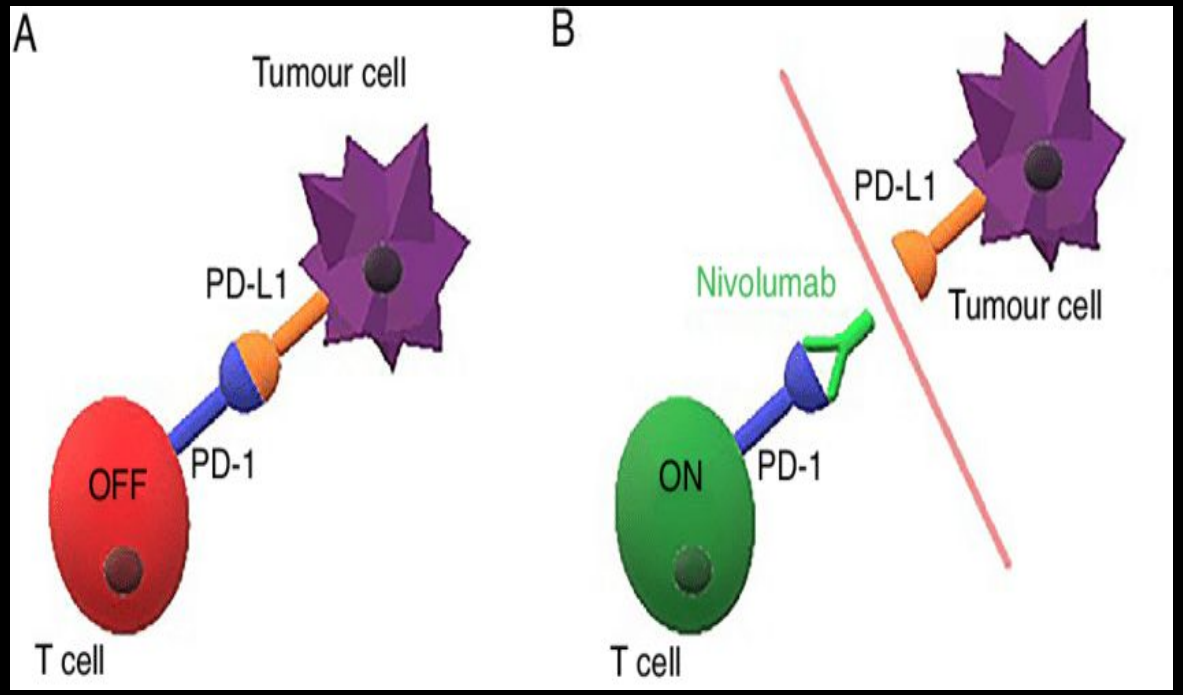
The PD-1:PD-L1/2 interaction directly inhibits apoptosis of the tumor cell, promotes peripheral T effector cell exhaustion, and promotes conversion of T effector cells to Treg cells



Additional cells such as NK cells, monocytes, and dendritic cells also express PD-1 and/or PD-L1

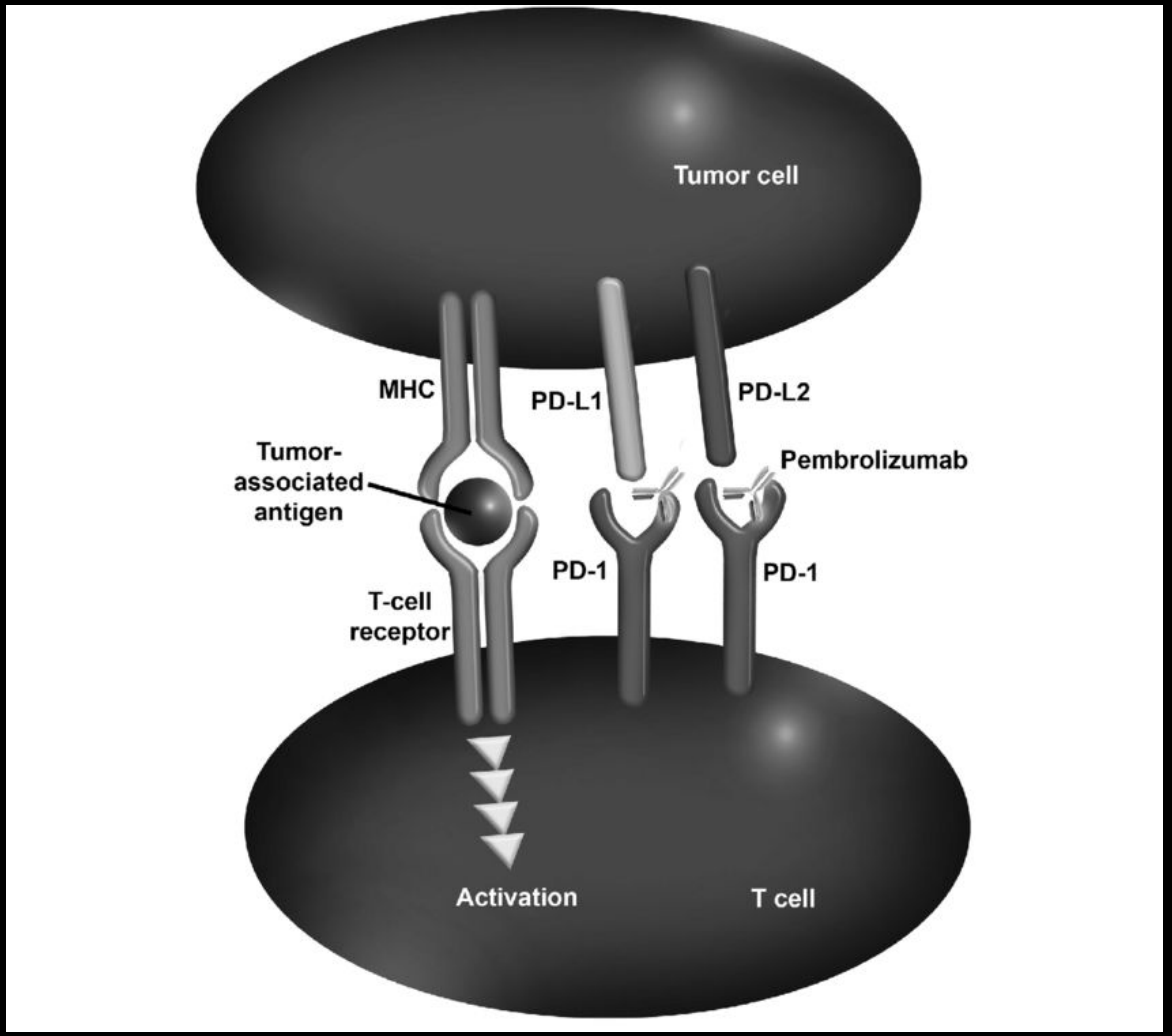
Immunotherapy

- **Nivolumab** is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding to its receptor



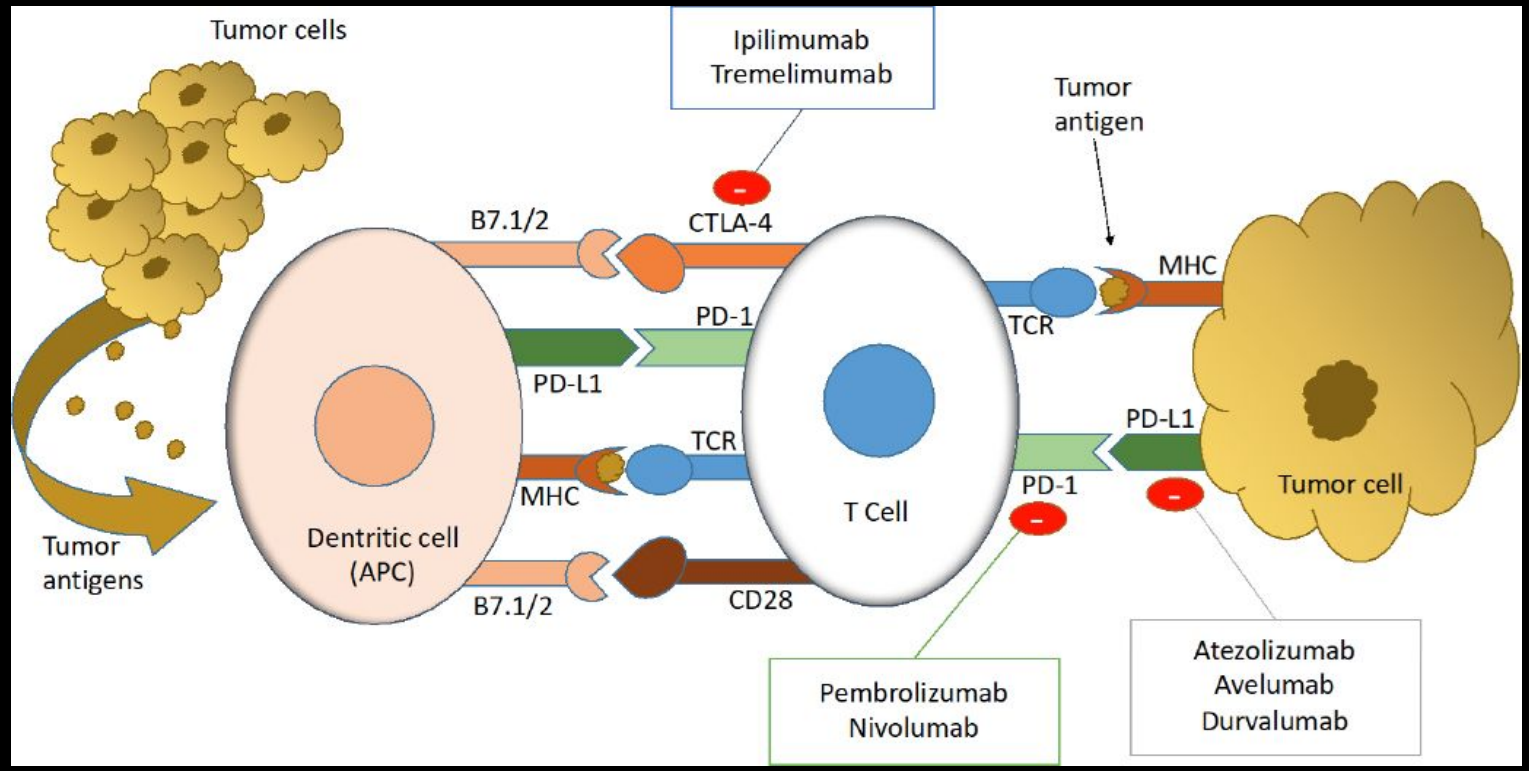
Immunotherapy

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1 receptor, blocking of ligands PD-L1 and PDL-2 from interaction with PD-1 to help to restore T-cell response



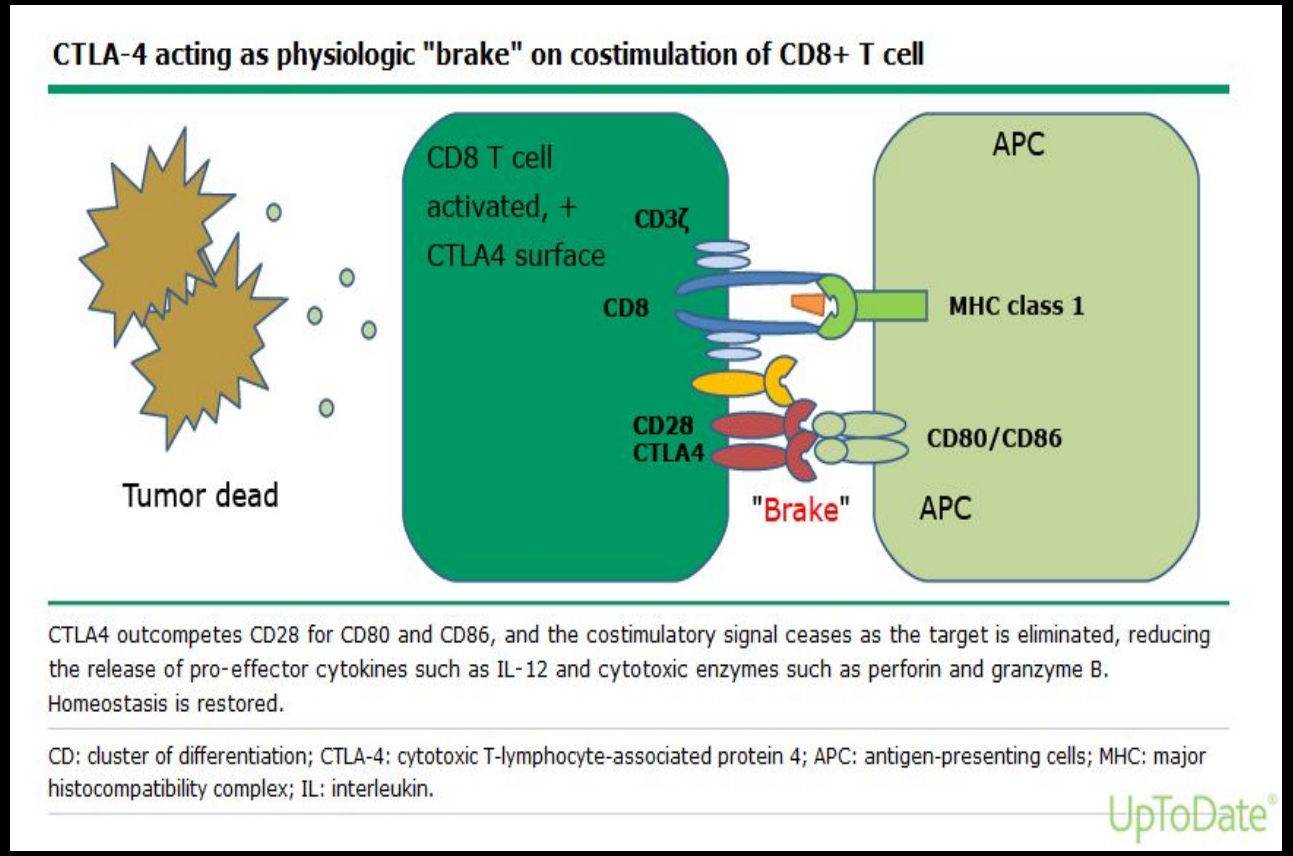
Immunotherapy

- **Avelumab** is a fully human monoclonal antibody that binds to programmed death ligand 1 (PD-L1) to selectively prevent the interaction between the programmed cell death-1 (PD-1) and B7.1 receptors, while still allowing interaction between PD-L2 and PD-1



Immunotherapy

- **Ipilimumab** is a recombinant human IgG1 immunoglobulin monoclonal antibody that binds to the cytotoxic T-lymphocyte associated protein 4, which is a down-regulator of T-cell activation pathways



Blocking CTLA-4 allows for enhanced T-cell activation and proliferation

Immunotherapy combinations

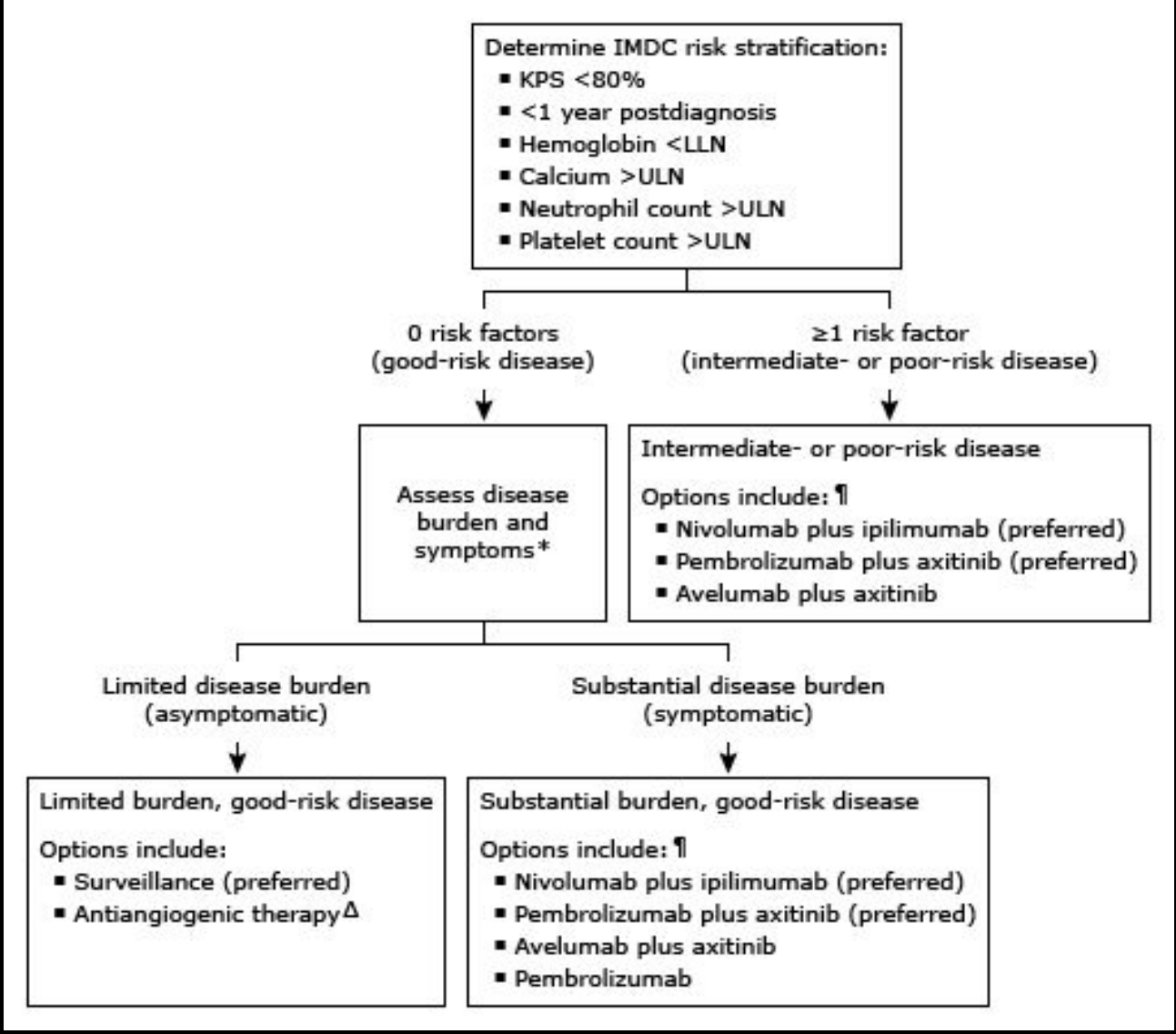
- Combining nivolumab (anti-PD-1) with ipilimumab (anti-CTLA-4) results in enhanced T-cell function, resulting in improved anti-tumor responses in metastatic RCC

Another effective combinations for treatment of metastatic RCC?

Immunotherapy+ tyrosine kinase inhibitors

- **Nivolumab+cabozantinib**
- **Pembrolizumab+lenvatinib**
- **Pembrolizumab+axitinib**
- **Avelumab+axitinib…**

Approach to initial systemic therapy in patients with metastatic clear cell RCC



Patients with advanced or metastatic clear cell RCC are typically treated with systemic therapy as initial treatment. The decision to start systemic therapy and the selection of agent(s) depend on disease-related symptoms, patient comorbidities, and tumor risk stratification. Listed treatments are preferred options, although alternative agents that are not listed may also be effective. Clinical trials are encouraged if available.
Select patients may be candidates for cytoreductive nephrectomy prior to initiation of immunotherapy

RCC: renal cell carcinoma; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky performance status; LLN: lower limit of normal; ULN: upper limit of normal.

*** Patients with limited disease on imaging are usually asymptomatic. However, the decision to treat must take into account multiple factors, including rate of growth, location of tumor (eg, proximity to vital organs with potential for damage), and symptoms.**

¶ For those who are ineligible for or choose to forego initial treatment with immunotherapy combinations, regardless of risk category, we offer antiangiogenic therapy with vascular endothelial growth factor (VEGF) inhibitors. The preferred agent depends on risk stratification and patient comorbidities

Δ For patients with good-risk, asymptomatic disease who desire a more aggressive management approach, options include sunitinib or pazopanib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ההקשבה!