RENAL CELL CARCINOMA

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

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ADDENDUM to the CHI Original Renal Cell Carcinoma Clinical Guidance - Issued June 2020

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Abbreviations

AS	Active Surveillance
ASCO	American Society of Clinical Oncology
BAP1-TPDS	BAP1 Tumor Predisposition Syndrome
BHDS	Birt-Hogg-Dubé Syndrome
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CKCF	Children's Kidney Cancer Foundation
CNS	Central Nervous System
COG	Children's Oncology Group
DD4A	Chemotherapy regimen of vincristine, dactinomycin and doxorubicin
EAU	European Association of Urology
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EE4A	Chemotherapy regimen of vincristine and dactinomycin
EL	Evidence Level
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FHWT	Familial Wilms Tumor
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAS	Haute Autorité de Santé (French National Authority for Health)
HD-IL2	High-Dose Interleukin-2
HERED-RCC-D	Hereditary Renal Cell Carcinoma with Dismorphic Features
HLRCC	Hereditary Leiomyomatosis and Renal Cell Carcinoma
HPRC	Hereditary Papillary Renal Carcinoma
HTA	Health Technology Assessment
ICI	Immune Checkpoint Inhibitor

IMDC	International Metastatic RCC Database Consortium
IO	Immuno-Oncology
IQWIG	Institute for Quality and Efficiency in Health Care (Germany)
IV	Intravenous
MET	Metastasis
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence (UK)
NSS	Nephron-Sparing Surgery
OS	Overall Survival
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PD-L1	Programmed Death-Ligand 1
PE	Prescribing Edits
PGL/PCC	Pheochromocytoma and Paraganglioma
RANK	Receptor Activator of Nuclear Factor Kappa-B
RCC	Renal Cell Carcinoma
RT	Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SFDA	Saudi Food and Drug Authority
SIOP	International Society of Paediatric Oncology
TKI	Tyrosine Kinase Inhibitor
TSC	Tuberous Sclerosis Complex
US	United States
USD	United States Dollar
VAD	Vinblastine, Dactinomycin, and Doxorubicin
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel-Lindau
WAI	Whole Abdominal Irradiation
WT	Wilms Tumor

Executive Summary

Renal cell carcinoma (RCC) is a type of kidney cancer that originates in the cells of the renal tubules, which are part of the filtration system of the kidneys. It involves the uncontrolled growth of malignant cells in the lining of the renal tubules. These cancerous cells can form tumors within the kidneys and may also spread to other parts of the body over time. Renal cell carcinoma is known for its diverse subtypes, each with distinct characteristics, and it often presents a challenge in terms of diagnosis and treatment. Some patients with renal cell carcinoma do not have symptoms (asymptomatic) while others present with a wide range of symptoms including hematuria, abdominal mass, persistent flank pain, anorexia, unexplained weight loss and anemia[1].

There are several types of kidney cancer:

- **Renal Cell Carcinoma:** Representing approximately 85% of adult kidney cancer diagnoses, this type primarily emerges in the proximal renal tubules, integral components of the kidney's filtration system. Each kidney houses numerous of these minuscule filtration units. Further discussion on treatment options for renal cell carcinoma is elaborated later in this guide.
- **Urothelial Carcinoma (Transitional Cell Carcinoma):** Constituting 5% to 10% of diagnosed kidney cancers in adults, urothelial carcinoma initiates in the renal pelvis—the region where urine accumulates before entering the bladder. Treatment for this kidney cancer mirrors that of bladder cancer, as both originate in the cells lining the renal pelvis and bladder.
- **Sarcoma:** A rare occurrence, sarcoma of the kidney manifests in the soft tissue, the capsule enveloping the kidney, or adjacent fat. Surgical intervention is typically employed for sarcoma treatment; however, recurrence in the kidney area or dissemination to other body parts is common, necessitating potential supplementary surgery or chemotherapy following the initial procedure.
- **Wilms Tumor:** Predominantly affecting children, Wilms tumor comprises around 1% of kidney cancers. Diverging from the adult counterpart, this tumor type responds more favorably to a combination of surgery, radiation therapy, and chemotherapy. This distinctive approach has evolved due to its efficacy in treatment.
- **Lymphoma:** Lymphoma can lead to the enlargement of both kidneys and is linked with swollen lymph nodes (lymphadenopathy) in various body regions such as the neck, chest, and abdominal cavity. While kidney lymphoma

occasionally presents as a solitary tumor mass, a biopsy may be performed to confirm the diagnosis (see Diagnosis), and chemotherapy, rather than surgery, may be recommended if lymphoma is suspected[2].

RCC is a complex condition influenced by a combination of genetic, mechanical, and environmental factors. Several risk factors can increase an individual's likelihood of developing Renal Cell Carcinoma. These risk factors include:

- **Age:** The risk of renal cell carcinoma increases with age, with most cases diagnosed in individuals over 40.
- **Gender:** Men are more likely to develop renal cell carcinoma than women.
- **Smoking:** Cigarette smoking is a significant risk factor for kidney cancer.
- **Obesity:** People who are overweight or obese have a higher risk of developing renal cell carcinoma.
- **Hypertension:** Chronic high blood pressure may increase the risk.
- **Family History:** A family history of kidney cancer can elevate the risk.
- **Certain Genetic Conditions:** Hereditary conditions like Von Hippel-Lindau (VHL) syndrome and hereditary papillary renal cell carcinoma can predispose individuals to kidney cancer[3].

Some of the complications and related problems associated with Renal Cell Carcinoma include:

- **Metastasis:** Renal cell carcinoma has a propensity to spread to other organs and tissues. Common sites for metastasis include the lungs, bones, liver, and brain. Metastatic spread can significantly impact the prognosis and treatment approach.
- **Inferior Vena Cava (IVC) Invasion**: In advanced cases, the tumor may invade the inferior vena cava, the large vein that carries deoxygenated blood from the lower body back to the heart. This can lead to complications such as blood clots or impaired blood flow.
- **Paraneoplastic Syndromes:** Renal cell carcinoma may produce substances that cause systemic effects on the body, known as paraneoplastic syndromes. These can include anemia, hypercalcemia (elevated calcium levels), and polycythemia (increased red blood cell count), among others.
- **Renal Vein Thrombosis:** Blood clots may form in the renal veins due to the tumor's impact on blood circulation. Renal vein thrombosis can cause pain and may lead to complications such as pulmonary embolism if the clot travels to the lungs.

- **Renal Failure:** In some cases, especially when both kidneys are affected or in the presence of extensive tumor burden, renal cell carcinoma can lead to renal failure. This occurs when the kidneys lose their ability to function adequately, resulting in the accumulation of waste products and fluid imbalances.
- **Hypertension (High Blood Pressure):** Renal cell carcinoma can contribute to the development or exacerbation of hypertension. This may occur due to the tumor's impact on the renal arteries or the production of substances that affect blood pressure regulation.
- **Recurrence:** Even after successful treatment, there is a risk of cancer recurrence. Regular follow-up and monitoring are essential to detect and manage any recurrence promptly[4].

RCC represents around 3% of all cancers, with the highest incidence occurring in Western countries. Worldwide, the year 2020 witnessed an estimated 431,288 individuals being diagnosed with kidney cancer. In 2023, approximately 81,800 adults in the United States (US) are expected to receive a kidney cancer diagnosis, comprising 52,360 men and 29,440 women. In the US, kidney cancer ranks as the sixth most prevalent cancer among men and the ninth most common among women. The typical age at which individuals are diagnosed with kidney cancer is 64, with the majority receiving diagnoses between the ages of 65 and 74. Kidney cancer is relatively uncommon in individuals under the age of 45 but exhibits a higher incidence among Black people and American Indian people. Over the past few decades, there has been a continual rise in the incidence of new kidney cancer cases in the United States. However, this upward trend has shown a deceleration in recent years, with rates increasing by 1% annually between 2010 and 2019. A contributing factor to this increase is the more widespread utilization of imaging tests, which may incidentally detect small kidney tumors during examinations conducted for reasons unrelated to cancer[5,6].

Although RCC is a common malignancy and its incidence is increasing, there is little information concerning the disease in Saudi Arabia. The latest cancer registry report in 2013 showed that renal cancer is the tenth most common cancer and has an age-standardized rate (ASR) of 2.4/100,000, accounting for 2.3% of all cancers. The incidence has increased by 33%, with most cases presenting late in the disease course. However, there are currently no national cancer control programs aimed at early detection and prevention[7].

The burden of disease associated with RCC includes various factors such as pain, discomfort, healthcare costs, and potential complications. RCC is associated with substantial economic burden, although the estimates are wide ranging. The

literature reported annual estimates of the US economic burden of RCC between $US0.60 billion and $US5.19 billion, with per-patient costs of $US16 488-43 805[8]. Kidney cancers are one of the most important cancers, due in part to the large economic burden of metastatic kidney cancer, which has been estimated to be $1.6 billion (2006 USD) in selected countries and to globally account for more than 131,000 deaths and 342,000 incident cases each year[9].

Drug therapy is an integral component for the management of Renal Cell Carcinoma. The goals of treating RCC include complete removal of tumor (curative intent), preventing recurrence, slowing disease progression (advanced or metastatic disease), palliative care, preserving kidney function (partial nephrectomy), improving overall survival, and enhancing quality of life[10].

The treatment of RCC depends on several factors, including the stage of the cancer, the overall health of the patient, and the specific characteristics of the tumor. Treatment modalities may include:

- **Surgery:**
    - **Nephrectomy:** Surgical removal of the affected kidney is a common treatment for localized RCC. Depending on the extent of the cancer, this may involve partial nephrectomy (removing only the tumor and part of the kidney) or radical nephrectomy (removing the entire kidney).
- **Targeted Therapies:**
    - **Tyrosine Kinase Inhibitors (TKIs):** Medications such as sunitinib, pazopanib, and axitinib target specific molecules involved in the growth of cancer cells. They are commonly used in advanced or metastatic RCC.
- **Immunotherapy:**
    - **Immune Checkpoint Inhibitors:** Drugs like nivolumab, pembrolizumab, and atezolizumab enhance the body's immune response against cancer cells. They are particularly effective in some cases of advanced RCC.
- **Combination Therapies:**
    - **Combining Targeted Therapies and Immunotherapy:** In certain cases, a combination of targeted therapies and immunotherapy may be used to enhance treatment effectiveness.
- **Radiation Therapy:**

    - **External Beam Radiation:** Directed radiation may be used to target and shrink tumors. It is often employed for palliative purposes or to manage symptoms in cases where surgery is not feasible.
- **Ablation Techniques:**
    - **Cryoablation and Radiofrequency Ablation:** Minimally invasive procedures that use extreme cold (cryoablation) or high-frequency energy (radiofrequency ablation) to destroy cancer cells. These may be considered for small tumors or in situations where surgery is not an option.
- **Palliative Care:**
    - For individuals with advanced or metastatic RCC, palliative care focuses on symptom management, pain relief, and improving the patient's quality of life[10].

CHI issued Renal Cell Carcinoma clinical guidance after thorough review of renowned international and national clinical guidelines in June 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Renal Cell Carcinoma clinical guidance and seeks to offer guidance for the effective management of Renal Cell Carcinoma. It provides an **update on the Renal Cell Carcinoma Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely **European Society for Medical Oncology** (ESMO) Clinical Practice Guidelines for Renal Cell Carcinoma **(2020-2021)** and **National Comprehensive Care Network** (NCCN) Kidney Cancer (**v1.2024**).

Moreover, **new guidelines are added to the report** such as:

- **Saudi Oncology Society and Saudi Urology Association** combined clinical management guidelines for renal cell carcinoma **(2017)**
- **National Comprehensive Care Network** (NCCN) Wilms Tumor **(v1.2023)**
- **American Society of Clinical Oncology** (ASCO) Management of Metastatic Clear Cell Renal Cell Carcinoma **(2022-rapid 2023 update)**
- **European Association of Urology** (EAU) Guidelines on Renal Cell Carcinoma **(2023)**

- **Canadian Kidney Cancer Forum** (CKCF) Consensus Statement on Adjuvant Chemotherapy for Renal Cell Carcinoma **(2023)**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that there has been **withdrawal** of the following drug: ranitidine.

Moreover, there has been **several FDA/EMA approved drug** for the treatment of Renal Cell Carcinoma:

Table 1. Added Drugs for the Treatment of Renal Cell Carcinoma (RCC)

DRUGS	SFDA STATUS
Avelumab	Registered
Belzutifan	Registered
Tivozanib	Not registered
Savolitinib	Not registered
Temsirolimus	Not registered

Table 2. Added Drugs for the Treatment of Wilms Tumor

DRUGS	SFDA STATUS
Dactinomycin	Not registered

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in RCC were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The use of **Avelumab** is backed by some HTA bodies as HAS[11], IQWIG[12] and PBAC[13] with positive recommendations. However, it has a negative recommendation by NICE[14] for use in RCC. The use of **Belzutifan** is backed by some HTA bodies as CADTH[15] with a conditional recommendation. There is no HTA data regarding the use of **cyclophosphamide, doxorubicin, etoposide, and vincristine** in Wilms Tumor. Nevertheless, they have been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

Additionally, there have been **updates** regarding previously mentioned drugs in terms of drug information and prescribing edits since June 2020.

Table 3. Prescribing Edits (PE) Modifications for Kidney Cancer Medications

Drugs	PE modifications
Axitinib	Add AGE: no approved for use in pediatric patients. Add PE: used as part of a chemotherapy protocol as monotherapy or in combination with pembrolizumab or avelumab.
Bevacizumab	Remove PA. Add ST: not a preferred treatment option; other contemporary therapies have replaced the use of bevacizumab in the treatment of renal cell carcinoma. Add PE: used as part of a chemotherapy protocol, as monotherapy or as part of a combination regimen.
Cabozantinib	Add AGE: for use in children ≥ 12 years of age, adolescents, and adults. Add PE: used as part of a chemotherapy protocol, as monotherapy or as part of a combination regimen. Modify PA: should be prescribed by a medical oncologist for the treatment of RCC in adult patients, as part of chemotherapy protocol either as monotherapy or as part of a combination regimen, in patients with advanced RCC.
Carboplatin (RCC)	Add CU: carboplatin should be used in combination with paclitaxel or gemcitabine. Used in combination with anti-emetic agents. Add PE: used per protocols mentioned regarding combination options and sequence of therapy. Add ST: carboplatin is typically not considered a first-line treatment for RCC; considered in later lines of therapy.
Carboplatin (Wilms tumor)	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: recommended for relapsed/refractory disease.
Cisplatin	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: cisplatin is not typically considered a first-line treatment for renal cell carcinoma (RCC). Considered in later lines of therapy
Cyclophosphamide	Remove PA.

	Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add QL: for IV: some experts recommend no exceeding 1000mg/dose. For oral: 150 mg/day. Add ST: not usually the first-line treatment.
Doxorubicin	Remove PA. Add QL: cumulative lifetime limit: 400 mg/m^2 Add PE: part of a chemotherapy treatment protocol
Erlotinib	Remove PA. Add ST: not a standard first-line treatment for RCC. Considered in later lines of therapy, particularly in patients with advanced or metastatic RCC who have failed previous treatments. Add AGE: not approved for use in pediatric patients.
Etoposide	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: recommended for relapsed/refractory disease.
Everolimus	Remove PA. Add PE: used as part of a treatment protocol (most commonly in combination with Lenvatinib); can be used as monotherapy.
Gemcitabine	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: gemcitabine is not typically considered a first-line treatment for renal cell carcinoma (RCC). considered in later lines of therapy.
Ipilumab	Add CU: ipilimumab should be used in combination with nivolumab. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add PA: ipilimumab should be prescribed by a medical oncologist in combination with nivolumab (for a maximum of 4 combination doses) as first-line treatment in patients with poor/intermediate risk stage IV RCC, or as second-line treatment in patients with favorable risk stage IV RCC.

	Add QL: administer for a maximum of 4 combination doses (ipilimumab + nivolumab); followed by nivolumab monotherapy.
Lenvatinib	Remove PA, ST. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy.
Mesna	Add PE: used as part of a chemotherapeutic protocol.
Nivolumab	Remove PA. Add PE: used as part of a chemotherapy protocol, either as monotherapy or in combination with ipilimumab or Cabozantinib.
Paclitaxel	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: Paclitaxel is not typically considered a first-line treatment for renal cell carcinoma. Considered in later lines of therapy.
Pazopanib hydrochloride	Remove PA. Add AGE: not approved for use in pediatric patients. Add ST: used as a 2nd line option in patients with stage IV disease.
Pembrolizumab	Add PE: used per protocols combination options either ad monotherapy or in combination with axitinib or lenvatinib & sequence of therapy.
Sorafenib	Remove PA. Add ST: used as a 3rd line option in recurrent RCC post nephrectomy. Add AGE: not approved for use in pediatric patients.
Sunitinib	Remove PA. Add AGE: not approved for use in pediatric patients.
Vincristine	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Influenza therapeutic management.

Below is a table summarizing the major changes based on the different guidelines on the management of RCC and Wilms tumor used to issue this report:

Table 4. General Recommendations for the Management of Renal Tumors

Management of Renal Cell Carcinoma		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**

Surgical management
• Consider nephron-sparing surgery (partial nephrectomy) for specific patient groups, including:
  ○ Unilateral stage I–III tumors when technically feasible
  ○ Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
  ○ Patients at a relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (e.g., hypertension, diabetes, nephrolithiasis)
  ○ In cases where partial nephrectomy is not possible, a radical nephrectomy is considered and should be determined by tumor size, location, and the overall health of the patient.
	2A[16]
	EL1[17]
	Strong recommendation[18]
		NCCN[16]
		Saudi Oncology Society and Saudi Urology Association[17]
		EAU[18]

For potentially surgically resectable tumor: consider tissue sampling and primary treatment with • Cytoreductive nephrectomy in select patients Or • Systemic therapy (preferred in clear cell histology with poor-risk features)	2A[16]	NCCN[16]

For surgically unresectable tumor: consider systemic therapy		
For potentially surgically resectable tumor: Potentially resectable primary tumors with solitary metastasis or multiple resectable lung metastases: these patients should undergo primary nephrectomy and resection of the metastatic lesion/s.	EL2[17]	Saudi Oncology Society and Saudi Urology Association[17]
Following complete resection, no further therapy or "adjuvant therapy" is indicated.	EL3[17]	
Potentially resectable primary and multiple non-resectable metastases: these patients should undergo resection of the primary tumor if in good performance status (EL 1), then start systemic therapy: ○ **Clear cell histology with good or intermediate risk**: options of therapy include systemic therapy with either sunitinib (EL 1), bevacizumab and interferon α 2a, or pazopanib (EL 1). ○ High-dose interleukin-2 may be used in highly selected patients and centers. ○ **Clear cell histology with poor risk:** temsirolimus is the preferred treatment (EL 1). An alternative option is sunitinib (EL 2). ○ **Non-clear cell histology:** options of therapy include temsirolimus (EL 2), sunitinib (EL 2), or sorafenib (EL 2). Medullary and collecting duct	Each level listed next to the drugs	Saudi Oncology Society and Saudi Urology Association[17]

carcinomas should be treated with platinum-based chemotherapy (EL 3).		

Stage IV kidney cancer: Clear cell histology: treated with
• Clinical trial
or
• **first line therapies for favorable risk**:
  • Axitinib + pembrolizumab (category 1)
  • Cabozantinib + nivolumab (category 1)
  • Lenvatinib + pembrolizumab (category 1)
or
• **first line therapies for poor/intermediate risk**:
  ○ Axitinib + pembrolizumab (category 1)
  ○ Cabozantinib + nivolumab (category 1)
  ○ Ipilimumab + nivolumab (category 1)
  ○ Lenvatinib + pembrolizumab (category 1).
  It is worth noting that this combination remains superior to sunitinib on clinical outcomes as first-line treatment for advanced renal cell carcinoma as observed by the CLEAR trial[19].
  ○ Cabozantinib
or
• Metastasectomy
or
• stereotactic body radiation therapy (SBRT)
or
	2A[16]	NCCN[16]

• ablative techniques for oligometastatic disease or • Metastasectomy with complete resection of disease, followed by adjuvant pembrolizumab within 1 year of nephrectomy and • **Best supportive care**: include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases (offered for patients only if not fit for systemic treatment).		
Stage IV kidney cancer: Non-clear cell histology: treated with: • Clinical trial or cabozantinib (preferred) Or • **Lenvatinib + pembrolizumab** is suggested as first-line treatment for patients with non-clear cell RCC, regardless of histology, based on results from the Keynote-B61 trial[20]. • **Other recommended systemic therapy regimens:** o Lenvatinib + everolimus o Nivolumab o Nivolumab + cabozantinib o Pembrolizumab o Sunitinib or • Metastasectomy or • SBRT or	2A[16] Not graded[20]	NCCN[16] *Lancet Oncol*. 2023[20]

• ablative techniques for oligometastatic disease and • **Best supportive care**		
Active surveillance is a viable option for the initial management of patients with clinical stage T1 renal lesions, including: • Small renal masses < 3 cm, given the high rates of benign tumors and low metastatic potential. • Active surveillance is recommended for patients with T1a tumors (≤ 4 cm) that have a predominantly cystic component. • Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.	2A[16]	NCCN[16]
Management of local/locoregional disease **Systemic treatment for clear cell renal cell carcinoma** The combination of PA should be considered as a front-line therapeutic option for patients with advanced disease, irrespective of IMDC prognostic subgroups and PD-L1 biomarker status while the combination of IN should be considered as a first-line option in patients with IMDC intermediate- and poor-risk disease.	I, A[21–24]	ESMO[21–24]
VEGF-targeted therapy is recommended in those patients where pembrolizumab/axitinib or ipilimumab/nivolumab are not available or are contraindicated.	I, A–II, B[21–24]	ESMO[21–24]
Adjuvant therapy in clear cell renal cell carcinoma For patients at intermediate or high risk operable clear cell RCC (ccRCC), adjuvant	IC[21–24] Not graded[25]	ESMO[21–24] CKCF[25]

Pembrolizumab could be considered as an option after careful patient counselling regarding immature Overall survival (OS) and potential long-term adverse events. Treatment initiation should occur within 12 weeks post-surgery and continue for up to 1 year.		
Adjuvant therapy in clear cell renal cell carcinoma For patients with stage III disease, clear cell histology and a high risk for relapse, the use of adjuvant sunitinib is recommended.	3[16]	NCCN[16]
Patients who have undergone complete resection of their oligometastatic disease could be offered adjuvant pembrolizumab.	II, B[21–24]	ESMO[21–24]
Strongly discourage the use of adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong recommendation[18]	EAU[18]
Management of metastatic disease Cytoreductive nephrectomy may be offered to select patients with metastatic ccRCC	Evidence quality: High; Strength of recommendation: Strong[26,27]	ASCO[26,27]
Management of metastatic disease • Strongly advise against performing cytoreductive nephrectomy (CN) in MSKCC poor-risk patients. • Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong recommendation[18]	EAU[18]
Management of metastatic disease **First-line treatment for advanced ccRCC** • Lenvatinib–pembrolizumab has gained FDA approval but not EMA approval. It's now included among other combinations targeting VEGFR and PD-1 inhibitors (such as axitinib–pembrolizumab or cabozantinib–nivolumab recommended as initial treatment for advanced ccRCC,	I, A[21–24] Strong recommendation[18]	ESMO[21–24] EAU[18]

regardless of IMDC risk groups. No specific preference is indicated among VEGFR TKI–PD-1 inhibitor combinations.		
Management of metastatic disease **Single-agent targeted therapy** Strongly recommend offering nivolumab or cabozantinib for immune checkpoint inhibitor-naive, vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong recommendation[18]	EAU[18]
Management of metastatic disease **First-line treatment for advanced ccRCC** Ipilimumab–nivolumab remains the recommended first-line treatment for IMDC intermediate- and poor-risk disease.	I, A[21–24] Evidence quality: High; Strength of recommendation: Strong[26,27]	ESMO[21–24] ASCO[26,27]
Management of metastatic disease **First-line treatment for advanced ccRCC** Patients with favorable-risk disease requiring systemic therapy may be offered an ICI in combination with a VEGFR TKI.	Evidence quality: High; Strength of recommendation: Strong[26,27]	ASCO[26,27]
Management of metastatic disease **First-line treatment for advanced ccRCC** Sunitinib, pazopanib and tivozanib are options if immunotherapy is not suitable or available for first-line combinations.	I, A[21–24] for sunitinib/pazopanib II, B[21–24] for tovizanib	ESMO[21–24]
Management of metastatic disease **First-line treatment for advanced ccRCC** Cabozantinib is also an alternative for IMDC intermediate- and poor-risk disease in patients unable to receive first-line PD-1 inhibitor-based therapy.	II, A[21–24]	ESMO[21–24]
Management of metastatic disease **First-line treatment for advanced ccRCC**	I, D[21–24]	ESMO[21–24]

In the first-line setting, only ICI-based combinations that demonstrate a survival advantage are recommended. Axitinib–avelumab and bevacizumab–atezolizumab, as they don't show an OS advantage, are not recommended.		
Management of metastatic disease **First-line treatment for advanced ccRCC** Lenvatinib–everolimus is not considered a standard initial treatment for metastatic disease. It can be recommended as subsequent therapy after the initial treatment alongside other agents.	I, D[21–24]	ESMO[21–24]
	III, B[21–24]	
Management of metastatic disease The use of high-dose interleukin-2 (HD-IL2) may be considered in the first-line systemic therapy setting for patients with metastatic ccRCC. Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful.	Evidence quality: Moderate; Strength of recommendation: Weak[26,27]	ASCO[26,27]
Management of metastatic disease It is strongly advised against administering IpiNivoCabo treatment to patients with metastatic clear cell renal cell carcinoma (ccRCC). Individuals expressing interest in triplet therapy are encouraged to participate in a clinical trial.	Evidence quality: high; Strength of recommendation: Strong[26,27]	ASCO[26,27]
Metastatic disease: **Second- or later-line systemic treatment for ccRCC** Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone.	Evidence quality: high; Strength of recommendation: Strong[26,27] Strong recommendation[18]	ASCO[26,27] EAU[18]
Metastatic disease: **Second- or later-line systemic treatment for ccRCC**	Evidence quality: Moderate; Strength of	ASCO[26,27] FDA[28,29]

• Patients progressing on combination immunotherapy (e.g., nivolumab and ipilimumab) should be offered a VEGFR TKI. • Patients who progress after initial therapy combining VEGFR TKI with an ICI may be offered an alternate VEGFR TKI as a single agent. • On December 14, 2023, the FDA approved belzutifan for patients with advanced renal cell carcinoma (RCC) following PD-1 or PD-L1 inhibitor and a VEGF-TKI.	recommendation: Strong[26,27] Evidence quality: High; Strength of recommendation: Strong[26,27]	
Medical treatment for advanced/metastatic papillary RCC • Cabozantinib is the recommended initial treatment for advanced papillary RCC without further molecular testing. • Other choices include sunitinib, pembrolizumab without additional molecular testing, and savolitinib (if accessible) for tumors driven by MET alterations.	II, B[21–24] for cabozantinib, sunitinib Weak recommendation[18] III, B[21–24] for pembrolizumab III, C[21–24] for savolitinib	EAU[18] ESMO[21–24]
Metastatic RCC: Targeted therapy in non-clear-cell RCC Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak recommendation[18]	EAU[18]
Management of Wilms Tumor		
For most children with suspected WT, **surgery** is recommended, even for those initially considered unresectable or with bilateral or metastatic disease. Risk assessment helps determine the need for and type of adjuvant therapy after surgery. Unilateral nephrectomy is often performed upfront for children with resectable unilateral kidney disease.	2A[30]	NCCN[30]

Surgery • Most patients with favorable histology WT undergo unilateral radical ureteronephrectomy, while nephron-sparing surgery (NSS) is reserved for bilateral disease, genetically predisposed individuals, or those at higher risk for renal failure. • NSS is not recommended for unilateral disease without genetic predisposition.	2A[30]	NCCN[30]
Chemotherapy • Chemotherapy is proven to enhance the survival of most children with Wilms tumor (WT) when combined with surgery, with or without radiotherapy. • Various chemotherapy regimens, such as EE4A, DD4A, VAD, regimen M, and regimen I, are employed. Although some agents overlap, the schedules differ, and certain regimens serve for neoadjuvant or adjuvant purposes.	2A[30]	NCCN[30]
Neoadjuvant chemotherapy • Neoadjuvant chemotherapy regimens are employed for patients who cannot undergo upfront nephrectomy. • Options include EE4A, DD4A, or VAD.	2A[30]	NCCN[30]
Adjuvant Chemotherapy • Regimens for adjuvant chemotherapy encompass: EE4A, DD4A, regimen M, and regimen I. • The specific regimens employed depend on the context and risk stratification.	2A[30]	NCCN[30]
Radiation Therapy Adjuvant RT is recommended for higher-risk patients post-surgery but is not	2A[30]	NCCN[30]

indicated for those with low-stage, lower-risk disease. RT should start by day 10 after surgery but no later than day 14. Coordination between RT and chemotherapy is essential to avoid concurrent administration of full doses of dactinomycin or doxorubicin with RT allowing for the administration of these agents at full doses prior to RT.		

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Renal Cell Carcinoma clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts; the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Renal Cell Carcinoma report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

The following segment contains the updated versions of the guidelines mentioned in the June 2020 CHI Renal Cell Carcinoma Report and the corresponding recommendations:

Table 5. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Renal Cell Carcinoma **(2019)**	eUpdate **07 February 2020:** New Renal Cell Carcinoma Treatment Recommendations
	eUpdate **26 February 2020:** New Renal Cell Carcinoma Treatment Recommendations
	eUpdate **30 November 2020:** Recent eUpdate to the ESMO Clinical Practice Guidelines on Renal Cell Carcinoma (RCC)
	eUpdate **28 September 2021:** Update on the use of Immunotherapy in Early Stage and Advanced Renal Cell Carcinoma
1.2 National Comprehensive Care Network (NCCN) Kidney Cancer **(v2.2020)**	**National Comprehensive Care Network** (NCCN) Kidney Cancer (**v1.2024**)
1.3 Children Oncology Group (COG) Wilms Tumor Guidelines **(2019)**	Not available

1.4 International Society of Pediatric Oncology (SIOP) Guidelines **(2019)**	Not available

1.1.1 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Renal Cell Carcinoma (eUpdates 2020-2021)

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for the management of RCC in 2019. In 2020 and in 2021, several eUpdates were published, leading to several modification or additional recommendations[21–24]. These updates are detailed below.

Table 6. ESMO Clinical Guidelines Grading/Level of Evidence

Level of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendations	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Management of local/locoregional disease

Systemic treatment for clear cell renal cell carcinoma

- The combination of pembrolizumab and axitinib (PA) should be considered as a front-line therapeutic option for patients with advanced disease, irrespective of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic subgroups and PD-L1 biomarker status [I, A], while the combination of ipilimumab and nivolumab (IN) should be considered as a first-line option in patients with IMDC intermediate- and poor-risk disease [I, A].
- VEGF-targeted therapy is recommended in those patients where pembrolizumab/axitinib or ipilimumab/nivolumab are not available or are contraindicated [I, A–II, B].
- There is limited data for treatment after progression or intolerance on PA or IN. VEGF TKIs are the recommended treatment for these patients [III, B].

Adjuvant therapy in clear cell renal cell carcinoma

- For patients at intermediate or high risk operable clear cell RCC (ccRCC) (as defined by the study). Adjuvant Pembrolizumab could be considered as an option after careful patient counselling regarding immature overall survival (OS) and potential long-term adverse events [I,C]. Treatment initiation should occur within 12 weeks post-surgery and continue for up to 1 year.
- In the case of the M1 NED population, for patients who experience a relapse within a year of nephrectomy, the established treatment involves using programmed cell death protein 1 (PD-1)-based combination therapy [I, A]. Considering metastasectomy as an alternative to this systemic therapy for patients with synchronous or early oligometastatic disease is generally not recommended [I, D] and requires a decision from a multidisciplinary team.
- Patients who have undergone complete resection of their oligometastatic disease could be offered adjuvant pembrolizumab [II, B].
- However, offering incomplete resection to patients with oligometastatic disease is not advisable [III, D].

Management of metastatic disease

First-line treatment for advanced ccRCC

- Lenvatinib–pembrolizumab [I, A] has gained FDA approval but not EMA approval. It's now included among other combinations targeting VEGFR and PD-1 inhibitors (such as axitinib–pembrolizumab [I, A] or cabozantinib–

nivolumab [I, A] recommended as initial treatment for advanced ccRCC, regardless of IMDC risk groups. No specific preference is indicated among VEGFR TKI–PD-1 inhibitor combinations and comparing across different trials indirectly is discouraged [I, D].

- Ipilimumab–nivolumab remains the recommended first-line treatment for IMDC intermediate- and poor-risk disease [I, A].
- Immunotherapy-based treatment shows notable effectiveness in sarcomatoid renal tumors and is strongly recommended over using a single-agent VEGFR TKI [II, A].
- Sunitinib [I, A], pazopanib [I, A], and tivozanib [II, B] are options if immunotherapy is not suitable or available for first-line combinations. Cabozantinib [II, A] is also an alternative for IMDC intermediate- and poor-risk disease in patients unable to receive first-line PD-1 inhibitor-based therapy.
- In IMDC favorable-risk disease, sunitinib or pazopanib could be considered alternatives to PD-1 inhibitor-based combination therapy due to the lack of clear superiority of PD-1-based combinations over sunitinib in this patient subgroup [I, B].
- Surveillance might be an option for a small group of patients but needs careful consideration [III, C].
- In the first-line setting, only ICI-based combinations that demonstrate a survival advantage are recommended. Axitinib–avelumab and bevacizumab–atezolizumab, as they don't show an OS advantage, are not recommended [I, D].
- Discontinuing ICIs should be considered after two years of therapy [IV, C].
- Lenvatinib–everolimus is not considered a standard initial treatment for metastatic disease [I, D], but it can be recommended as subsequent therapy after the initial treatment alongside other agents [III, B].

After disease progression on PD-1 inhibitor-based combination therapy for ccRCC

- Continuing treatment with a VEGFR TKI after initial PD-1 inhibitor-based therapy shows moderate response rates and is suggested as the usual practice [III, B]. However, these findings come from less-than-ideal studies. The selected VEGFR-targeted medication should be one they haven't used before [III, B].

- There isn't enough randomized evidence to back the continuation of immune checkpoint inhibitors after progression from initial therapy, so this approach is not advised [IV, D].

Medical treatment for advanced/metastatic papillary RCC

- Cabozantinib is the recommended initial treatment for advanced papillary RCC without further molecular testing [II, B]. Other choices include sunitinib [II, B], pembrolizumab [III, B] without additional molecular testing, and savolitinib (if accessible) for tumors driven by MET alterations [III, C].
- In the second-line, priority should be given to medications not previously administered in the first-line treatment [IV, C]. In some cases where systemic therapy lacks substantial data, selected patients may consider best supportive care [IV, C].

New therapies/indications in renal cell carcinoma:

- For advanced RCC after prior VEGF-targeted therapy: Cabozantinib can be used.
- Cabozantinib plus nivolumab are considered as first-line treatment of advanced RCC.
- For Advanced or metastatic RCC following one prior VEGF-targeted therapy: Lenvatinib plus everolimus is considered.
- Lenvatinib plus pembrolizumab are considered as first-line treatment of advanced RCC.
- For Treatment of advanced RCC after failure of one or two regimens of antiangiogenic therapy, recommend Nivolumab.
- Nivolumab plus ipilimumab are used for first-line treatment of intermediate-/poor-risk advanced RCC.
- Pembrolizumab plus axitinib are used for first-line treatment of advanced clear cell RCC.
- Tivozanib is used as the first targeted therapy in recurrent or metastatic RCC with a clear cell component.

Table 7. International Metastatic RCC Database Consortium (IMDC) Score

Adverse risk factor	Limit
Reduced Karnofsky Index	<80%
Elevated neutrophils	> upper limit of normal
Elevated platelets	> upper limit of normal
Low hemoglobin	below the lower limit of normal
Elevated corrected calcium	> 10 mg/dl or 2,4 mmol/l
Time from nephrectomy to metastases formation	below one year
Interpretation	
Low risk (0 risk factors)	Median overall survival of 43 months
Intermediate risk (1-2 risk factors)	Median overall survival of 23 months
High risk (3 or more risk factors)	Median overall survival of 8 months

1.1.2 National Comprehensive Care Network (NCCN) Kidney Cancer (v 1.2024)

The main recommendations from the NCCN clinical practice guidelines of the management of kidney cancer (v 1.2024) are summarized below[16].

Table 8. NCCN Clinical Guidelines Grading/Level of Evidence

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
All recommendations are Category 2A unless otherwise indicated	

Table 9. Tumor, Node, and Metastasis (TNM) Staging

Primary tumor (T) Metastasis (M)	Regional lymph nodes (N)	Distant

TX: Primary tumor cannot be assessed T0: No evidence of primary tumor T1: Tumor ≤7 cm, limited to the kidney T1a: Tumor ≤4 cm, limited to the kidney T1b: Tumor >4 cm, but ≤7 cm in greatest dimension T2: Tumor >7 cm in greatest dimension, limited to the kidney T2a: Tumor >7 cm but ≤10 cm in greatest dimension T2b: Tumor >10 cm, limited to the kidney T3: Tumor extends into major veins or directly invades adrenal gland or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia T3a: Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or tumor invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia T3b: Tumor grossly extends into the vena cava below the diaphragm T3c: Tumor grossly extends into vena cava	NX: Regional lymph node(s) cannot be assessed N0: No regional lymph node metastasis N1: Metastasis in a single regional lymph node N2: Metastasis in more than one regional lymph node	M0: No distant metastasis M1: Distant metastasis

above the diaphragm or invades the wall of the vena Cava T4a: Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		

Table 10. American Joint Committee on Cancer (AJCC) Prognostic Groups

Stage grouping	T stage	N stage	M stage
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-T2 T3	N1 NX, N0-N1	M0 M0
Stage IV	T4 Any T	Any N Any N	M0 M1

The first-line treatment options for stage I, II, and III kidney cancer typically include surgical interventions, such as: **Nephrectomy** which is the surgical removal of the affected kidney is the primary treatment for localized renal cancer. This may involve removing only the tumor (partial nephrectomy) or the entire kidney (radical nephrectomy).

- **Partial Nephrectomy (PN):** This approach is preferred when feasible, especially for smaller tumors or cases where preserving kidney function is crucial. It involves removing only the tumor, leaving the rest of the kidney intact.
- **Radical Nephrectomy (RN):** In cases where partial nephrectomy is not possible, a radical nephrectomy involves removing the entire kidney along with surrounding tissues and lymph nodes.
- The choice between partial and radical nephrectomy depends on factors such as tumor size, location, and the overall health of the patient.

General principles of management for renal cell carcinoma

- Consider nephron-sparing surgery (partial nephrectomy) for specific patient groups, including:
    - Unilateral stage I–III tumors when technically feasible
    - Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
    - Patients at a relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (e.g., hypertension, diabetes, nephrolithiasis)
- Radical and partial nephrectomies can be performed using open, laparoscopic, or robotic surgical techniques.
- Optional regional lymph node dissection is recommended for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at the time of surgery.
- Adrenalectomy may be omitted if the adrenal gland is uninvolved.
- Specialized teams or referral to high-volume centers may be necessary for cases with extensive inferior vena cava involvement.
- Thermal ablation methods (e.g., cryosurgery, radiofrequency ablation, microwave ablation) are viable options for managing clinical stage T1 renal lesions.
    - Thermal ablation is a consideration for clinical T1b masses in select patients ineligible for surgery.
    - Biopsy of lesions is recommended before or during ablation.
    - Ablative techniques may require multiple treatments to achieve comparable local oncologic outcomes to conventional surgery.
- Stereotactic body radiation therapy (SBRT) is viewed as an ablative therapy and may be considered for medically inoperable patients (not optimal surgical candidates) with stage I (category 2B), II, or III (both category 3) kidney cancer.
- Active surveillance is a viable option for the initial management of patients with clinical stage T1 renal lesions, including:
    - Small renal masses <3 cm, given the high rates of benign tumors and low metastatic potential.
    - Active surveillance is recommended for patients with T1a tumors (≤4 cm) that have a predominantly cystic component.

    - Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
    - Active surveillance involves serial abdominal imaging with timely intervention if the mass shows changes indicative of increasing metastatic potential.
    - Periodic metastatic surveys, including blood work and chest imaging, are recommended during active surveillance.
- Generally, patients suitable for cytoreductive nephrectomy before systemic therapy should have:
    - Excellent performance status (ECOG PS <2)
    - No brain metastasis
- Patients with large-volume distant metastases or tumors with substantial sarcomatoid burdens should receive systemic therapy before cytoreductive nephrectomy.

Table 11. Management of Kidney Cancer According to the Staging of the Disease

Stage I (T1a) kidney cancer management	
Partial nephrectomy (**preferred**) Or Ablative techniques Or Active surveillance Or Radical nephrectomy (in select patients)	**Adjuvant treatment:** Surveillance
Stage I (T1b) kidney cancer management	
Partial nephrectomy Or Radical nephrectomy Or Active surveillance (in select patients) Or Ablative techniques (in select patients)	**Adjuvant treatment:** Surveillance
Stage II kidney cancer management	
Partial nephrectomy	**Adjuvant treatment:**

Or Radical nephrectomy	Adjuvant pembrolizumab (grade 4 tumors with clear cell histology +/- sarcomatoid features) Or Surveillance
Stage III kidney cancer management	
Radical nephrectomy Or Partial nephrectomy, if clinically indicated	**Adjuvant treatment:** *Clear cell histology:* Adjuvant pembrolizumab or Surveillance or Adjuvant sunitinib (category 3) *Non-clear cell histology:* Surveillance or Clinical trial
Stage IV kidney cancer management	
For potentially surgically resectable tumor: consider tissue sampling and primary treatment with • Cytoreductive nephrectomy in select patients Or • Systemic therapy (preferred in clear cell histology with poor-risk features)	For surgically unresectable tumor: consider **systemic therapy** (will be discussed below)

For stage IV kidney cancer or relapsing disease, tissue sampling may yield the following:

1. **Clear cell histology:** treated with
    - Clinical trial

      or
    - first line therapies (tables 11 and 12)

      or

- Metastasectomy

  or

- stereotactic body radiation therapy (SBRT)

  or

- ablative techniques for oligometastatic disease

  or

- Metastasectomy with complete resection of disease, followed by adjuvant pembrolizumab within 1 year of nephrectomy

  and

- Best supportive care: include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases.

2. **Non-clear cell histology:** treated with:

- Clinical trial (preferred)

  or

- Systemic Therapy (table 13)

  or

- Metastasectomy

  or

- SBRT

  or

- ablative techniques for oligometastatic disease

  and

Best supportive care

Table 12. First-Line Treatment Options for Relapse/Stage IV Kidney Cancer (Clear Cell Histology)

Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable	• Axitinib + pembrolizumab (category 1) • Cabozantinib + nivolumab (category 1) • Lenvatinib + pembrolizumab (category 1)	• Axitinib + avelumab • Cabozantinib (category 2B) • Ipilimumab + nivolumab • Pazopanib • Sunitinib	• Active surveillance • Axitinib (category 2B) • High-dose IL-2d (category 2B)
Poor/ intermediate	• Axitinib + pembrolizumab (category 1) • Cabozantinib + nivolumab (category 1) • Ipilimumab + nivolumab (category 1) • Lenvatinib + pembrolizumab (category 1) • Cabozantinib	• Axitinib + avelumab • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2 for patients with excellent performance status and normal organ function (category 3) • Temsirolimus (category 3)
All recommendations are category 2A unless stated otherwise.			

Table 13. Subsequent Treatment Options for Relapse/Stage IV Kidney Cancer (Clear Cell Histology)

Immuno-oncology (IO) Therapy History Status	Preferred regimens	Other recommended regimens	Useful in certain circumstances
IO Therapy Naïve	None	• Axitinib + pembrolizumab • Cabozantinib • Cabozantinib + nivolumab	• Axitinib • Everolimus • Pazopanib

		• Ipilimumab + nivolumab • Lenvatinib + everolimus • Lenvatinib + pembrolizumab • Nivolumab	• Sunitinib • Tivozanib (For patients who received ≥ 2 prior systemic therapies) • Belzutifan (category 2B) • Bevacizumab (category 2B) (An FDA-approved biosimilar is an appropriate substitute for bevacizumab) • High-dose IL-2 for selected patients (Patients with excellent performance status and normal organ function) (category 2B) • Temsirolimus (category 2B) • Axitinib + avelumab (category 3)
Prior IO Therapy	None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib	• Axitinib + pembrolizumab • Cabozantinib + nivolumab • Everolimus • Ipilimumab + nivolumab • Lenvatinib + pembrolizumab • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab (category 2B) (An FDA-approved biosimilar is an appropriate substitute for bevacizumab)

			• High-dose IL-2 for selected patients (Patients with excellent performance status and normal organ function) (category 2B) • Temsirolimus (category 2B) • Axitinib + avelumab (category 3)

All recommendations are category 2A unless stated otherwise.

Table 14. Systemic Therapy Options for Relapse/Stage IV Kidney Cancer (Non-Clear Cell Histology)

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Clinical trial • Cabozantinib	• Lenvatinib + everolimus • Nivolumab • Nivolumab + cabozantinib • Pembrolizumab • Sunitinib	• Axitinib • Bevacizumab* • Bevacizumab* + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Bevacizumab* + everolimus • Erlotinib • Everolimus • Nivolumab + ipilimumab (category 2B) • Pazopanib • Temsirolimus (category 1 for poor-prognosis risk group; category 2A for other risk groups) **: An FDA-approved biosimilar is an appropriate substitute for bevacizumab*

All recommendations are category 2A unless stated otherwise.

HEREDITARY RENAL CELL CARCINOMA

- Preoperative caution: Individuals suspected or diagnosed with PGL/PCC or VHL face an elevated risk of PCCs and should undergo blood and/or urine screening before any surgical procedure.
- ***BAP1*-Tumor Predisposition Syndrome (TPDS):** Surgical management guidelines for this syndrome are currently missing.
- **Birt-Hogg-Dubé syndrome (BHDS):** For renal tumors, nephron-sparing surgery is the preferred treatment whenever feasible, acknowledging the potential for multiple tumors in an individual's lifetime. Ablative treatment options can be considered for those with substantial medical or surgical risks.
- **Hereditary leiomyomatosis and renal cell cancer (HLRCC):** Due to the aggressive nature of tumors associated with HLRCC, surveillance is not recommended, and total radical nephrectomy should be considered.
- **Hereditary papillary renal carcinoma (HPRC):** In cases of HPRC, nephron-sparing surgery is the preferred treatment for renal tumors when possible, considering the potential for multiple tumors in an individual's lifetime. Ablative treatment options can be considered for those with significant medical or surgical risks.
- **Paraganglioma (PGL)/pheochromocytoma (PCC):** Surgical resection is recommended for malignant tumors with non-aggressive histology and early stages, with partial nephrectomy as an option. For larger tumors or those with aggressive histology, such as high grade or sarcomatoid features, radical nephrectomy is recommended.
- **Tuberous sclerosis complex (TSC):** Angiomyolipoma, a benign lesion associated with TSC, is managed separately. Nephron-sparing surgery is the preferred treatment for malignant renal tumors, with consideration for multiple tumors over an individual's lifetime. Ablative treatment options can be considered for those with significant medical or surgical risks.
- **Von Hippel-Lindau (VHL):** The management of localized renal masses in VHL patients typically follows the "3 cm rule." Intervention aims to balance the prevention of metastatic disease with the consideration of recurrent and multiple resections leading to chronic and progressive renal failure. Partial nephrectomy is recommended if possible, and referral to centers with expertise in complex partial nephrectomies and comprehensive care of VHL patients should be considered. Ablative treatment options can be considered for those with significant medical or surgical risks.

Table 15. Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC

Syndrome	Kidney-Specific Systemic Therapy
HLRCC	Useful in Certain Circumstances • Erlotinib plus bevacizumab[a,b]
TSC	Useful in Certain Circumstances • Everolimus[c]
VHL	Preferred Regimen • Belzutifan[d] Useful in Certain Circumstances • Pazopanib

All recommendations are category 2A unless otherwise indicated.

[a] An FDA-approved biosimilar is an appropriate substitute for bevacizumab

[b] There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC.

[c] Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.

[d] Belzutifan is FDA-approved for the treatment of VHL-associated RCC, central nervous system (CNS) hemangioblastomas, or pNET, not requiring immediate surgery.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Renal Cell Carcinoma report, along with their recommendations.

Table 16. List of Additional Guidelines

Additional Guidelines
Saudi Oncology Society and Saudi Urology Association Combined Clinical Management Guidelines for Renal Cell Carcinoma **(2017)**
American Society of Clinical Oncology (ASCO) Guideline on the Management of Metastatic Clear Cell Renal Carcinoma **(2022)** + Rapid Recommendation Update **(2023)**
European Association of Urology (EAU) Guidelines on Renal Cell Carcinoma (**2023**)
Canadian Kidney Cancer Forum (CKCF) Consensus Statement on Adjuvant Chemotherapy for Renal Cell Carcinoma (**2023**)

National Comprehensive Care Network (NCCN) Wilms Tumor (**v 1.2023**)

1.2.1 Saudi Oncology Society and Saudi Urology Association Combined Clinical Management Guidelines for Renal Cell Carcinoma (2017)

This guideline published jointly by the Saudi Oncology Society and the Saudi Urology Association aim to update the previously published Saudi guidelines for the evaluation and medical and surgical management of renal cell carcinoma[17]. The main recommendations are summarized below.

Table 17. Grading the Certainty of Evidence and Strength of Recommendations of the Saudi Oncology Society and Saudi Urology Association Guideline

Evidence level		Description of evidence quality
Evidence level 1 (EL 1)	Highest level	Evidence from phase III randomized trials or meta-analyses
Evidence level 2 (EL 2)	Intermediate level	Evidence from good phase II trials or phase III trials with limitations
Evidence level 3 (EL 3)	Low level	Evidence from retrospective or observational data and/or expert opinion

Localized disease (T1a)

- Surgical excision, preferably through partial nephrectomy (open, laparoscopic, or robotic), is the recommended treatment for all cases, particularly in patients with a solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency (EL 1).
- Reserve radical nephrectomy (preferably laparoscopic) for cases where partial nephrectomy is technically infeasible after consultation with an experienced surgeon (EL 1).
- Non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended, except for patients with significant comorbidities that prevent surgical intervention (EL 2).

Localized disease (T1b)

- The recommended treatment is radical nephrectomy (preferably laparoscopic) (EL 1).

- Partial nephrectomy may be considered, especially in patients with a solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency. However, this should only be performed by an experienced surgeon in a high-volume center (EL 1).
- Non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended.

Localized disease (T2)

- The recommended treatment is radical nephrectomy (EL 1).
- Partial nephrectomy and non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended.

Localized disease (T3)

- The recommended treatment is radical nephrectomy with complete excision of all venous thrombus in the renal vein, inferior vena cava, and right atrium (EL 2).
- These surgeries should only be performed in tertiary care centers with the availability of a cardiac, vascular, or hepatic surgeon, depending on the case (EL 2).

Excision of the ipsilateral adrenal gland

- Ipsilateral excision of the adrenal gland during radical nephrectomy is indicated in upper pole kidney tumors or the presence of a concurrent radiologically detectable adrenal gland lesion(s) (EL 2).

Lymph node dissection

- Resection of the regional lymph nodes (within Gerota's fascia) is an integral part of radical nephrectomy.
- Resection of non-regional lymph nodes provides no therapeutic advantages but is used for staging purposes (EL 1). When performing partial nephrectomy, the surgeon should aim to obtain an adequate surgical margin and avoid tumor inoculation, except in patients with von Hippel–Lindau syndrome.

Metastatic advanced, unresectable disease

- For risk stratification of metastatic RCC, two valid options are available (table 17):

    - The Memorial Sloan Kettering Cancer Center (MSKCC/Motzer) risk classification for metastatic disease
    - Heng Score for Metastatic RCC Prognosis.
- Potentially resectable primary tumors with solitary metastasis or multiple resectable lung metastases: these patients should undergo primary nephrectomy and resection of the metastatic lesion/s (EL 2). Following complete resection, no further therapy or "adjuvant therapy" is indicated (EL 3).
- Potentially resectable primary and multiple non-resectable metastases: these patients should undergo resection of the primary tumor if in good performance status (EL 1), then start systemic therapy according to the following guidelines:
    - Clear cell histology with good or intermediate risk: options of therapy include systemic therapy with either **sunitinib** (EL 1), **bevacizumab and interferon α 2a**, or **pazopanib** (EL 1).
    - High-dose interleukin-2 may be used in highly selected patients and centers.
    - Clear cell histology with poor risk: **temsirolimus** is the preferred treatment (EL 1). An alternative option is **sunitinib** (EL 2).
    - Non-clear cell histology: options of therapy include **temsirolimus** (EL 2), **sunitinib** (EL 2), or **sorafenib** (EL 2). Medullary and collecting duct carcinomas should be treated with platinum-based chemotherapy (EL 3).
    - Unresectable primary tumor with or without metastatic disease: These patients with good performance status should be offered systemic therapy according to their histological results and MSKCC risk group.
- Recurrent disease post-primary nephrectomy: treatment will depend on whether resectable or not:
    - If resectable solitary metastasis: surgical resection should be attempted (EL 2). No systemic therapy is of benefit following complete resection (EL 3).
    - If non-resectable recurrence: the patient should be treated as metastatic disease according to their histological results, using the MSKCC Risk Score and/or Heng Score.

- Second-line therapy post-tyrosine kinase inhibitor (TKI) failure: patients who fail with first-line TKIs should receive second-line therapy if in reasonable performance status. Options of second-line agents include **nivolumab** (EL 1), **cabozantinib** (EL 1), or **axitinib** (EL 1). In the absence of these options, **everolimus** can be considered.
- Third-line therapy: consider **everolimus** (EL 3), **sorafenib** (EL 3), or clinical trials.

Table 18. Metastatic Renal Cell Carcinoma Prognostic Models

Memorial Sloan Kettering Cancer Center (MSKCC) risk classification
Prognostic criteria
Time from diagnosis to treatment < 1 year
Hemoglobin < lower limit of normal
Calcium > 10 mg/dl (more than 2.5 mmol/L)
Lactate dehydrogenase > 1.5 x upper limit of normal
Karnofsky performance status < 80%
Risk stratification
Favorable risk: No prognostic factors
Intermediate risk: 1 or 2 prognostic factors
Poor risk: 3 prognostic factors
Heng risk classification
Prognostic criteria
Time from diagnosis to systemic treatment < 1 year
Hemoglobin < lower limit of normal
Calcium > 10 mg/dl (more than 2.5 mmol/L)
Karnofsky performance < than 80%
Neutrophil count > upper limit of normal
Platelets count > upper limit of normal
Risk stratification
Favorable risk: no prognostic factors
Intermediate risk: 1 or 2 prognostic factors
Poor risk: 3 or more prognostic factors

1.2.2 American Society of Clinical Oncology (ASCO) Guideline on the Management of Metastatic Clear Cell Renal Carcinoma (2022) + Rapid Update (2023)

The American Society of Clinical Oncology (ASCO) published clinical guidelines to provide recommendations for the management of patients with metastatic clear cell renal carcinoma (ccRCC) in 2022. The following year, a rapid update was published to update select recommendations[26,27]. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used for recommendations (table 19).

Table 19. GRADE Approach for Recommendations

Strength of Recommendation	
Strong	Benefits clearly outweigh risks and burden or vice versa. Usually stated as: **"we recommend"**
Conditional	Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.
Weak	Benefits closely balanced with risks and burden. Usually stated as: **"we suggest"**
Evidence Level (Quality of Evidence)	
High	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Medium	RCTs with important limitations (i.e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.

Low	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.
Very low	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

Diagnosis

- For the diagnosis of metastatic ccRCC, it is recommended to compare tissue obtained from outside the primary disease site with the primary histology. The histologic evaluation should include common markers of ccRCC, such as paired box gene 8 and carbonic anhydrase IX (Evidence quality: High; Strength of recommendation: Strong).
- In selected circumstances, radiographic diagnosis of metastatic ccRCC may be employed. This is particularly applicable in settings where a previous diagnosis of renal cell carcinoma has been established, when biopsy of metastatic tissue is not readily accessible, or when RECIST 1.1 measurable disease is evident, especially within a year of the initial diagnosis (Evidence quality: Low; Strength of recommendation: Weak).

Role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma

- Cytoreductive nephrectomy may be offered to select patients with metastatic ccRCC (Evidence quality: High; Strength of recommendation: Strong).

Preferred options for first-line systemic treatment of metastatic clear cell renal cell carcinoma

- For select patients with metastatic ccRCC, an initial active surveillance strategy may be offered (Evidence quality: Moderate; Strength of recommendation: Strong).
    - Select patients include those with IMDC favorable and intermediate risk, patients with limited or no symptoms related to disease, a favorable histologic profile, a long interval between nephrectomy and the development of metastasis, or with a limited burden of metastatic disease.

- All patients with metastatic ccRCC requiring systemic therapy in the first-line setting should undergo risk stratification into IMDC favorable (0), intermediate (1-2), and poor risk groups. Patients with intermediate- or poor-risk disease should be offered combination treatment with **two immune checkpoint inhibitors** (ICIs; i.e., ipilimumab and nivolumab) or an **ICI in combination with a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI)**; Evidence quality: High; Strength of recommendation: Strong).
- Patients with favorable-risk disease requiring systemic therapy may be offered an **ICI in combination with a VEGFR TKI** (Evidence quality: High; Strength of recommendation: Strong).
- Select patients with metastatic ccRCC receiving systemic therapy in the first-line setting, including those with favorable-risk disease or with certain coexisting medical problems, may be offered **monotherapy with either a VEGFR TKI or an ICI** (Evidence quality: Moderate; Strength of recommendation: Strong).
- The use of high-dose interleukin-2 (HD-IL2) may be considered in the first-line systemic therapy setting for patients with metastatic ccRCC. Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful (Evidence quality: Moderate; Strength of recommendation: Weak).
    - The significant toxicity of this regimen must be weighed in relation to the newer immunotherapy regimens that have largely replaced this treatment. The Expert Panel was not able to identify a patient population who should receive this treatment preferentially based on available data. The Expert Panel did agree that HD-IL-2 should be administered in experienced high-volume centers, and that enrollment in clinical trials was preferred.

Recommendation added from the 2023 update:

- *It is strongly advised against administering IpiNivoCabo treatment to patients with metastatic clear cell renal cell carcinoma (ccRCC). Individuals expressing interest in triplet therapy are encouraged to participate in a clinical trial (Evidence quality: High; Strength of recommendation: Strong).*

Optimal second- or later-line systemic treatment for metastatic clear cell renal cell carcinoma

- Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone (Evidence quality: High; Strength of recommendation: Strong).
- Patients progressing on combination immunotherapy (e.g., nivolumab and ipilimumab) should be offered a VEGFR TKI (Evidence quality: Moderate; Strength of recommendation: Strong).
- Patients who progress after initial therapy combining VEGFR TKI with an ICI may be offered an alternate VEGFR TKI as a single agent (Evidence quality: High; Strength of recommendation: Strong).
- For patients on immunotherapy who experience limited disease progression (e.g., one site of progression), local therapy (radiation, thermal ablation, and excision) may be offered, and immunotherapy may be continued (Evidence quality: Moderate; Strength of recommendation: Weak).

Optimal application of metastasis-directed therapy for metastatic clear cell renal cell carcinoma

- For patients with low-volume metastatic renal cell carcinoma, definitive metastasis-directed therapies may be offered and include surgical resection (metastasectomy), ablative measures, or radiotherapy (Evidence quality: Moderate; Strength of recommendation: Strong).
- For patients undergoing complete metastasectomy, subsequent TKIs are not routinely recommended (Evidence quality: Moderate; Strength of recommendation: Strong).

Considerations for treatment of special subsets of metastatic clear cell renal cell carcinoma (e.g., bone metastases, brain metastases, and sarcomatoid carcinomas)

- Patients with symptomatic bone metastases from metastatic ccRCC should receive bone-directed radiation (Evidence quality: Moderate; Strength of recommendation: Strong).
- Patients with bone metastases from metastatic ccRCC should be offered a bone resorption inhibitor (either bisphosphonate or receptor activator of nuclear factor kappa-B ligand inhibitor) when clinical concern for fracture or skeletal-related events is present (Evidence quality: Moderate; Strength of recommendation: Strong).

- No recommendation regarding optimal systemic treatment for metastatic ccRCC patients with bone metastasis can be made; however, it is our expert opinion that cabozantinib-containing regimens may be preferred (Evidence quality: Low; Strength of recommendation: Moderate).
- Patients with brain metastases from metastatic ccRCC should receive brain-directed local therapy with radiation therapy and/or surgery (Evidence quality: High; Strength of recommendation: Strong).
- No recommendation regarding optimal systemic therapy for patients with metastatic ccRCC and brain metastases can be made (Evidence quality: NA; Strength of recommendation: Strong).
- Patients with metastatic ccRCC with sarcomatoid features should receive ICI-based combination first-line treatment (ipilimumab plus nivolumab, or alternatively, an ICI plus a TKI; Evidence quality: High; Strength of recommendation: Strong).

1.2.3 European Association of Urology (EAU) Guidelines on Renal Cell Carcinoma (2023)

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC[18]. The main recommendations are summarized in table 21 below.

Table 20. Certainty of Evidence and Strength of Recommendations (EAU Guidelines)

Grade	Nature of recommendations
Strong recommendation (for/against)	Advantages of interventions clearly outweigh the disadvantages, or the disadvantages clearly outweigh the advantages
Weak recommendations (for/against)	Advantages and disadvantages of interventions are uncertain or the evidence regardless of its quality shows that the advantages and disadvantages are equal

Table 21. Summary of Recommendations for the Management of RCC (EAU Guidelines)

Recommendations	Strength
Treatment of localized RCC	

Provide surgical intervention for the purpose of achieving a cure in cases of localized renal cell cancer.	Strong
Recommend partial nephrectomy (PN) for individuals diagnosed with T1 tumors.	Strong
Consider PN for patients with T2 tumors who have a solitary kidney or chronic kidney disease, if technically feasible	Weak
Avoid performing ipsilateral adrenalectomy in the absence of clinical evidence indicating invasion of the adrenal gland.	Strong
Refrain from offering an extended lymph node dissection to patients with organ-confined disease.	Weak
Suggest embolization for individuals unfit for surgery who present with significant hematuria or flank pain.	Weak
Radical and partial nephrectomy techniques	
Recommend laparoscopic radical nephrectomy (RN) for individuals with T2 tumors and localized masses that cannot be treated with partial nephrectomy (PN).	Strong
Strongly advise against performing minimally-invasive RN in patients with T1 tumors when PN is feasible, regardless of the approach, including open surgery.	Strong
Avoid opting for minimally-invasive surgery if this approach may potentially compromise oncological, functional, and peri-operative outcomes.	Strong
Consider intensifying follow-up in patients with a positive surgical margin, particularly in those who have been upstaged to pT3a.	Weak
Therapeutic approaches as alternative to surgery	
Consider providing active surveillance (AS) or thermal ablation (TA) as options for frail and/or comorbid patients with small renal masses.	Weak
Prior to thermal ablation (TA), strongly recommend performing a percutaneous renal mass biopsy, and it should be conducted separately, not concomitantly with TA.	Strong
When offering TA or AS, engage in discussions with patients regarding the potential harms and benefits concerning oncological outcomes and complications.	Strong
Avoid routinely recommending TA for tumors larger than 3 cm and cryoablation for tumors exceeding 4 cm.	Weak

Treatment of locally advanced RCC	
As part of nephrectomy, extract clinically enlarged lymph nodes to assess staging, prognosis, and follow-up implications.	Weak
In cases of non-metastatic disease with venous involvement, strongly advocate for removing both the renal tumor and thrombus.	Strong
Engage in comprehensive discussions about treatment options for patients with locally-advanced unresectable renal cell carcinoma (RCC), considering biopsy, systemic therapy, deferred resection, or palliative management. This decision-making process should involve a multidisciplinary team to determine the treatment goal.	Strong
Neoadjuvant and adjuvant therapy	
Engage in discussions with patients to explore the contradictory results of available adjuvant immune checkpoint inhibitor (ICI) trials, facilitating shared decision-making.	Strong
Ensure patients are informed about the potential risks of overtreatment and immune-related side effects if adjuvant therapy is being considered.	Strong
Strongly discourage the use of adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
Avoid recommending adjuvant sunitinib for patients with surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak

Consider offering adjuvant pembrolizumab to ccRCC patients, preferably within 12–16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial:
• Intermediate-high risk:
  • pT2, grade 4 or sarcomatoid, N0, M0
  • pT3, any grade, N0, M0
• High risk:
  • pT4, any grade, N0, M0
  • any pT, any grade, N+, M0
  • M1 no evidence of disease (NED): NED after resection of oligometastatic sites < 1 year from nephrectomy.
	Weak

Advanced/metastatic RCC: local therapy	
Strongly advise against performing cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong

Avoid immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy.	Weak
Consider initiating systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy.	Weak
Encourage discussions about delayed CN with patients who experience clinical benefit from systemic therapy.	Weak
Consider immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak
Local therapy of metastases in metastatic RCC	
Consider providing ablative therapy, including metastasectomy, to patients with metastatic disease and favorable disease factors, ensuring complete resection is achievable, in order to control local symptoms.	Weak
Suggest stereotactic radiotherapy as an option for clinically relevant bone- or brain metastases to achieve local control and symptom relief.	Weak
Strongly discourage the use of tyrosine kinase inhibitor treatment for metastatic renal cell carcinoma (mRCC) patients after metastasectomy and in the absence of evidence of disease.	Strong
Before proceeding with metastasectomy, conduct a confirmatory axial scan of disease status to rule out rapidly progressive metastatic disease that may necessitate systemic treatment.	Weak
Prior to initiating systemic therapy for oligometastases that cannot be resected, engage in discussions with the patient about the possibility of observing the condition until progression is confirmed.	Weak
Systemic therapy in advanced/metastatic RCC	
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong
Single-agent targeted therapy in metastatic clear-cell RCC	
Strongly recommend offering nivolumab or cabozantinib for immune checkpoint inhibitor-naive, vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong

Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is advisable.	Weak
Consider VEGF-tyrosine kinase inhibitors as second-line therapy for patients refractory to nivolumab plus ipilimumab, axitinib plus pembrolizumab, cabozantinib plus nivolumab, or lenvatinib plus pembrolizumab.	Weak
Strongly recommend offering cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Emphasize the importance of sequencing systemic therapy in treating metastatic renal cell carcinoma (mRCC).	Strong
Consider immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
Immunotherapy in cc-mRCC	
Treatment-naïve patients	
Consider offering treatment with PD1 combinations in centers with experience to treatment-naïve patients	Weak
Strongly recommend offering either nivolumab plus ipilimumab, pembrolizumab plus axitinib, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naive patients with IMDC intermediate- or poor-risk disease.	Strong
Consider offering either pembrolizumab plus axitinib, lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naïve patients with IMDC favorable risk.	Weak
Consider offering sunitinib or pazopanib to treatment-naive patients with IMDC favorable risk.	Weak
Strongly recommend offering sunitinib or pazopanib to treatment-naive clear-cell metastatic renal cell carcinoma (cc-mRCC) patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
Strongly recommend offering cabozantinib to treatment-naive patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	Weak

Sequencing systemic therapy	
Strongly recommend sequencing systemic therapy in treating metastatic renal cell carcinoma (mRCC).	Strong
Consider offering VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Consider recommending sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy.	Weak
Strongly recommend offering nivolumab or cabozantinib to those patients who received first-line VEGF-targeted therapy alone.	Strong
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Strongly discourage re-challenging patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong
Targeted therapy in RCC with sarcomatoid features	
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
Targeted therapy in non-clear-cell metastatic RCC	
Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak
Targeted therapy in papillary metastatic RCC	
Consider offering cabozantinib to patients with papillary RCC (pRCC) based on a positive randomized controlled trial (RCT).	Weak
Consider offering pembrolizumab alone, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak
Locally recurrent RCC after treatment of localized disease	
Consider providing local treatment for locally recurrent disease when technically feasible, taking into account adverse prognostic features, comorbidities, and life expectancy.	Weak
Follow-up in RCC	
Recommend tailoring the follow-up after the treatment of localized RCC according to the risk of recurrence.	Strong

Consider intensifying follow-up in patients who undergo nephron-sparing surgery (NSS) for tumors larger than 7 cm or in those with a positive surgical margin.	Weak
Consider reducing the frequency of follow-up when the risk of death from other causes is twice that of the risk of RCC recurrence.	Weak

1.2.4 Canadian Kidney Cancer Forum (CKCF) Consensus Statement on Adjuvant Chemotherapy for Renal Cell Carcinoma (2023)

The objective of this consensus statement published by the Canadian Kidney Cancer Forum (CKCF) is to provide data-driven guidance regarding the use of ICIs after complete resection of clear-cell RCC[25]. The main recommendations are summarized below.

- Urologists should discuss the risk of cancer recurrence with patients who underwent surgery for RCC, utilizing validated prediction tools.
- For adjuvant therapy consideration, patients must have completely removed clear-cell RCC disease (localized, N+M0, or M1 NED).
- Patients with surgically removed clear-cell RCC, identified as having a heightened risk of recurrence, should be educated about the possible benefits of adjuvant therapy, and provided with the option of consulting a medical oncologist.
- Before initiating adjuvant therapy, patients should undergo staging that involves cross-sectional imaging of the chest, abdomen, and pelvis.
- In the event of administering adjuvant therapy, it should commence within 12–16 weeks following surgery.
- In the case of offering adjuvant therapy, pembrolizumab is presently the sole treatment recommended for consideration.
- Consideration for adjuvant systemic therapy may apply to patients with pT2 clear-cell RCC grade 4 or with sarcomatoid features, as well as those with pT3 clear-cell RCC disease.
- Patients with pT4 clear-cell RCC of any grade and those with N1 clear-cell RCC might be considered for adjuvant systemic therapy.
- Patients with resected M1 clear-cell RCC and no evidence of disease (NED) could be considered for adjuvant systemic therapy.

- If patients undergo adjuvant pembrolizumab, the treatment duration should last one year.
- During adjuvant therapy, patients should undergo follow-up imaging every 3–6 months.
- After completing adjuvant therapy, ongoing follow-up surveillance should follow guidelines for localized disease.
- Patients experiencing disease recurrence six months or more after finishing adjuvant therapy should be offered standard-of-care first-line treatment for metastatic disease.
- Patients experiencing disease recurrence during adjuvant therapy or within six months after completion should be managed similarly to patients progressing on first-line immunotherapy for metastatic disease.

1.2.5 National Comprehensive Care Network (NCCN) Wilms Tumor (v 1.2023)

The NCCN has issued the below recommendations for the treatment of Wilm tumor[30]:

Table 22. Children's Oncology Group (COG) Staging of Wilms Tumor

COG Staging of Wilms Tumor	
Stage I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. Note: For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria: • There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. Note: Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in

	Stage III.
Stage III	Residual nonhematogenous tumor present following surgery and confined to abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extraabdominal sites is a criterion for Stage IV.) • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurring either before or during surgery. • The tumor was biopsied (whether tru-cut, open or fine needle aspiration) before removal. • Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). Note: Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease

- Treatment for Wilms tumor (WT) varies and depends on several factors, including whether the tumor is unilateral or bilateral, its local stage, the presence of metastases, the patient's age, tumor weight, biologic risk factors, histology, and clinical response to therapy.

- A multidisciplinary evaluation involving surgeons, pediatric oncologists, and radiation oncologists is recommended before deciding on the treatment approach.
- For most children with suspected WT, **surgery** is recommended, even for those initially considered unresectable or with bilateral or metastatic disease. Risk assessment helps determine the need for and type of adjuvant therapy after surgery. Unilateral nephrectomy is often performed upfront for children with resectable unilateral kidney disease.
- While most cases involve resectable unilateral kidney disease, multifocal unilateral (10%) or primary bilateral renal tumors (5%–13%) are less common.
- **Treatment goals** aim to maximize cure while minimizing long-term toxicity. Long-term risks include secondary malignancy from chemotherapy and/or radiation therapy (RT), as well as the development of end-stage renal disease, among other concerns.

Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy is recommended for children with bilateral Wilms tumor (WT), initially unresectable unilateral tumors, or those with predisposing conditions and either localized or metastatic unilateral renal tumors.
- Specific chemotherapy regimens are administered for 6 weeks, followed by tumor response assessment.

Surgery

- Surgery for WT aims to remove all disease without tumor rupture, conduct accurate lymph node staging, and complete pathologic evaluation.
- Most patients with favorable histology WT undergo unilateral radical ureteronephrectomy, while nephron-sparing surgery (NSS) is reserved for bilateral disease, genetically predisposed individuals, or those at higher risk for renal failure.
- NSS is not recommended for unilateral disease without genetic predisposition.
- Surgical tissue specimens undergo testing for diagnosis confirmation, molecular markers, and histology, aiding risk stratification for appropriate adjuvant therapy.

- The decision on surgery type and timing, along with the need for neoadjuvant chemotherapy, is essential before treatment.
- Contraindications to upfront surgery include tumor extension to contiguous structures, solitary kidney, tumor thrombus above hepatic veins, unacceptable anesthesia risk, or significant pulmonary compromise.
- The clinical stage is determined before surgery, with confirmation and complete staging occurring after surgery.

Chemotherapy

- Chemotherapy is proven to enhance the survival of most children with Wilms tumor (WT) when combined with surgery, with or without radiotherapy.
- Various chemotherapy regimens, such as **EE4A, DD4A, VAD, regimen M**, and **regimen I**, are employed. Although some agents overlap, the schedules differ, and certain regimens serve for neoadjuvant or adjuvant purposes.
- The initiation of chemotherapy varies between NWTS studies and COG, but the total number of doses remains consistent.
- The specific duration and doses depend on the regimen.
- For example, in the EE4A regimen, 13 doses of vincristine and 7 doses of dactinomycin are administered over 18 weeks, while in the DD4A regimen, 15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin are given over 24 weeks.
- The choice of regimen is influenced by treatment response and the timing of surgery, with certain regimens reserved for neoadjuvant therapy in patients eligible for nephron-sparing surgery.
- Regimen M and regimen I have specific doses and schedules, and their initiation depends on factors such as molecular markers, lung metastasis response, or histology.

Chemotherapy Regimens

- **EE4A**: 13 doses of **vincristine** and 7 doses of **dactinomycin** administered over 18 weeks.
- **DD4A**: 15 doses of **vincristine**, 5 doses of **dactinomycin**, and 4 doses of **doxorubicin** (cumulative dose 150 mg/m2) administered over 24 weeks with alternating doses of dactinomycin and doxorubicin.

- **VAD**: 6–12 doses of **vincristine**, 2–4 doses of **dactinomycin**, and 2–4 doses of **doxorubicin** (cumulative dose 70–140 mg/m2) administered over 6–12 weeks used only in the neoadjuvant setting for patients who are candidates for NSS. In this regimen dactinomycin and doxorubicin are given together.7
- **Regimen M**: 9 doses of **vincristine**, 5 doses of **dactinomycin**, 5 doses of **doxorubicin** (cumulative dose 150 mg/m2), 4 cycles of 5 daily doses of **cyclophosphamide**, and 4 cycles of 5 daily doses of **etoposide** over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on molecular markers or response of lung metastases to 6 weeks of DD4A.
- **Regimen I**: 9 doses of **vincristine**, 4 doses of **doxorubicin** (cumulative dose 180 mg/m2), 7 cycles of 3 to 5 daily doses of **cyclophosphamide**, and 3 cycles of 5 daily doses of **etoposide**. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on histology.

Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy regimens are employed for patients who cannot undergo upfront nephrectomy.
- Options include **EE4A, DD4A, or VAD**.
- At the 6th week of neoadjuvant chemotherapy, reimaging assesses tumor resectability. Pulmonary lesions gauge chemotherapy response, with removal considered after 6 weeks if feasible.
- Complete response at week 6 eliminates the need for surgery, while less than partial response prompts an open biopsy for anaplasia or confirmation.
- For patients with partial response at week 6 but unsuitable for surgery, including nephron-sparing surgery (NSS), chemotherapy continues for 12 weeks. However, clinical trial data advise surgery by week 12, as prolonging chemotherapy beyond 12 weeks doesn't further reduce tumor size.

Adjuvant Chemotherapy

- Regimens for adjuvant chemotherapy encompass: **1) EE4A, 2) DD4A, 3) regimen M, and 4) regimen I.**
- The specific regimens employed depend on the context and risk stratification.

- For instance, children with unilateral favorable histology Wilms tumor (FHWT) at standard risk post-upfront nephrectomy are recommended to receive adjuvant chemotherapy with EE4A.
- The commencement of adjuvant chemotherapy should occur within 14 days following nephrectomy.
- As mentioned earlier, risk stratification guides the selection of the most suitable adjuvant chemotherapy regimens for patients.
- In cases where radiation therapy (RT) is necessary, the timing of adjuvant chemotherapy administration should be coordinated to prevent concurrent full doses of dactinomycin or doxorubicin with radiation.

Radiation Therapy

- For suspected Wilms tumor, the NCCN Panel advises early consultation with a radiation oncologist to allow sufficient time for potential radiation planning, coordinating with chemotherapy administration as necessary.
- Adjuvant RT is recommended for higher-risk patients post-surgery but is not indicated for those with low-stage, lower-risk disease.
- Depending on the scenario, recommendations may include adjuvant flank RT or Whole Abdominal Irradiation (WAI) with or without whole lung irradiation.
- For instance, adjuvant flank RT is suggested for patients with local stage III FHWT or stage IV with local stage III.
- It's crucial to note that biopsy alone does not elevate a tumor to stage III for determining the need for adjuvant RT. To enhance protection, testicular shielding is advised for most boys undergoing adjuvant flank RT.
- WAI is recommended for patients with cytology-positive ascites, any preoperative tumor rupture, peritoneal seeding, and diffuse surgical spillage.
- Supplementary boost irradiation is suggested for gross residual disease remaining after adjuvant flank RT or WAI.
- Adjuvant whole lung irradiation is indicated for patients with lung metastases, with the option of using intensity-modulated RT (IMRT) or anteroposterior/posteroanterior (AP/PA). However, in select patients with FHWT and lung-only metastases responding completely to 6 weeks of chemotherapy, whole lung irradiation may be omitted.
- Nevertheless, it remains recommended for patients with 1q gain or LOH at 1p and 16q.

- Studies emphasize the importance of starting RT within the initial 14 days post-surgery to reduce the risk of abdominal recurrence in metastasis-free patients.
- Ideally, the NCCN Panel suggests starting RT by day 10 after surgery but no later than day 14. Patient-specific factors, including age and the need to assess lung metastases response to chemotherapy when administering WAI and whole lung irradiation, should be considered.
- Coordination between RT and chemotherapy is essential to avoid concurrent administration of full doses of dactinomycin or doxorubicin with RT allowing for the administration of these agents at full doses before the initiation of RT.

Table 23. Treatment Options for Wilms Tumor

Unilateral renal tumor **Resectable**	**Very low risk** Children with FHWT fitting the criteria of the COG very-low-risk group can be observed without adjuvant therapy or receive adjuvant chemotherapy with EE4A. EE4A is recommended for children with very-low-risk clinical features but with unfavorable prognostic molecular markers (11p15 LOH or LOI or combined LOH at 1p and 16q). Observation only after surgery is recommended for children without these unfavorable biomarkers. Postoperative RT is not recommended for stage I disease. **Low risk** Children with FHWT at low risk after surgery can receive adjuvant therapy with regimen EE4A or switch to regimen DD4A. DD4A is recommended for children with low-risk tumors that express combined LOH 1p and 16q. EE4A can be continued for children with tumors that do not have these unfavorable biomarkers. Postoperative RT is not recommended for local stage I and II disease. **Standard risk and higher risk** DD4A is recommended for patients with stage III FHWT classified as standard risk after the initial risk assessment. At week 6 of DD4A, the results of molecular testing from diagnostic tissue are used to determine the final risk assessment and to select further therapy. Switching to augmented therapy with regimen M is recommended for

	patients with combined LOH of 1p and 16q who are at increased risk. Flank RT or WAI is recommended for patients with local stage III. If RT is being considered, the timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT. DD4A is the initial recommended therapy for higher-risk stage IV FHWT patients. At week 6 of DD4A, molecular testing and imaging results are utilized for the final risk assessment and treatment selection. Augmented therapy with regimen M is advised for patients with specific criteria, such as combined LOH of 1p and 16q or slow incomplete response of lung metastases after 6 weeks of chemotherapy. DD4A continues after week 6 for patients with lung-only metastases showing complete response or extrapulmonary metastases. However, regimen M is associated with increased toxicity risks, including second cancers and infertility. While a recent study switched patients with extrapulmonary metastases to regimen M (AREN0533), the results are pending publication, and this regimen is not currently recommended in this context. For patients with local stage III disease having higher risk, postoperative flank RT or WAI is recommended, and whole lung irradiation may be considered based on specific criteria, such as tumors expressing 1q gain or combined LOH at 1p and 16q. Whole lung irradiation is generally recommended for patients with pulmonary metastases, except for those with complete response of pulmonary lesions at 6 weeks and lacking certain risk factors.
Initially Unresectable Unilateral Renal Tumor with No Predisposing Condition	Neoadjuvant therapy with DD4A is recommended for initially unresectable unilateral renal tumors in children without predisposing conditions. Upfront biopsy, primarily in situations where upfront nephrectomy is contraindicated, is suggested for patients meeting delayed resection criteria, helping establish a WT diagnosis, determine histology, and gather molecular biomarkers for treatment guidance. At week 6 of DD4A, reimaging occurs, and based on tumor response, patients either undergo nephrectomy or continue with DD4A. Chemotherapy continues for 12 weeks if a patient responds but isn't a surgery candidate; however, surgery is

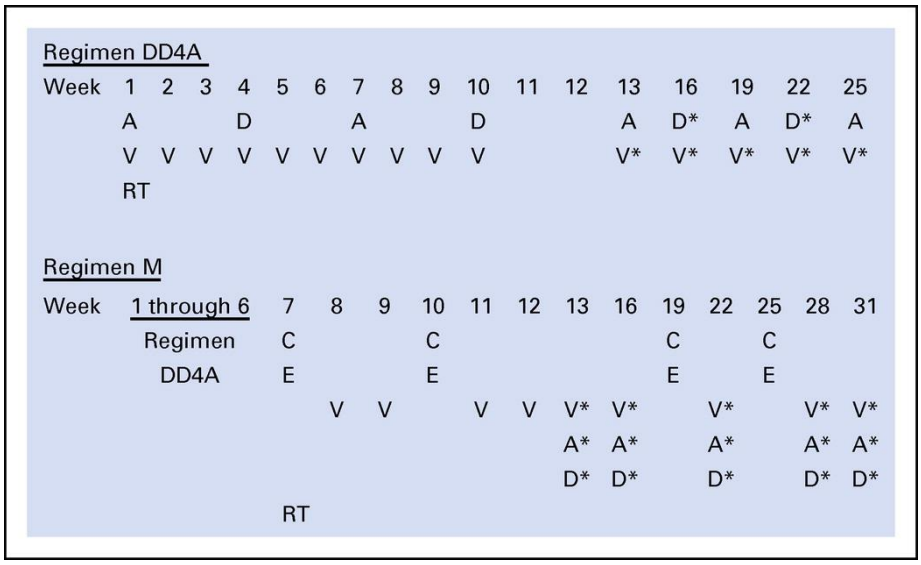
	recommended by week 12, as prolonged chemotherapy beyond this point typically doesn't further shrink tumors. After confirming FHWT pathology, molecular and imaging results guide the final risk assessment and therapy selection. Patients continue DD4A or switch to regimen M, particularly for those at increased risk, such as those with combined LOH at 1p and 16q or slow-responding lung metastases. While a recent study (AREN0533) switched patients with extrapulmonary metastases to regimen M, results are pending publication, and it's not currently recommended in this context. Postoperative flank RT or WAI is recommended for local stage III disease, and whole lung irradiation is advised in certain conditions, including lung metastases resistant to neoadjuvant chemotherapy and specific molecular characteristics. Coordination of RT timing with chemotherapy is crucial to avoid coadministration of full doses of dactinomycin or doxorubicin with RT.
Localized Unilateral Renal Tumor With a Predisposing Condition	Neoadjuvant therapy with the EE4A regimen is advised for children with a localized unilateral renal tumor and a predisposing condition, discouraging upfront biopsy or resection in this context. If upfront biopsy was performed, the VAD regimen is used for neoadjuvant therapy. At week 6 of EE4A (or VAD), depending on the response, patients may undergo no surgery with complete response, partial nephrectomy if the tumor is now resectable, continue with EE4A (or VAD) for 12 weeks if still unresectable but with partial response, or have complete nephrectomy if there's less than a partial response. If less than a partial response at week 6, a biopsy to confirm FHWT (or WT without anaplasia) is recommended before continuing with EE4A (or VAD). Surgery is performed at 12 weeks, as continuing chemotherapy beyond this period typically doesn't further shrink tumors. The decision for partial or total nephrectomy at week 12 depends on factors like tumor size, location, extension into the kidney collecting system, and other considerations.
Metastatic Unilateral Renal Tumor With a	Neoadjuvant therapy with the VAD regimen is recommended for children with a predisposing condition and a unilateral renal tumor that has metastasized,

Predisposing Condition	discouraging upfront biopsy or resection. At week 6 of VAD, based on the response, patients may undergo no surgery with complete response, partial nephrectomy if the tumor is now resectable, or continue with VAD for 12 weeks if the tumor is unresectable but with at least a partial response. If less than a partial response at week 6, a biopsy to confirm FHWT (or WT without evidence of anaplasia) is recommended before continuing with VAD. Surgery is performed at 12 weeks, as continuing chemotherapy beyond this period usually doesn't yield continued tumor shrinkage. A partial or total nephrectomy with regional lymph node sampling is recommended at week 12, depending on factors such as tumor size and location. After confirming FHWT, histology (blastemal predominant) is used to guide further therapy. Switching to regimen DD4A is recommended for patients without blastemal predominant histology or those with a complete response at 6 weeks. Augmented therapy with regimen I is recommended for patients with blastemal predominant histology due to their higher risk. Regimen M has not been studied in this population. The timing of radiation therapy (RT) is often 10 to 14 days after surgery, considering the patient's age and other factors. Local stage III, referring to the primary tumor staging regardless of metastases, determines the need for flank RT or WAI. Biopsy alone does not upstage a tumor to stage III. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting, and the omission of whole lung irradiation based on the response of lung metastases at week 6 of neoadjuvant chemotherapy has not been studied in this patient group.
Bilateral renal tumors	For children with **localized bilateral renal tumors**, neoadjuvant therapy using the VAD regimen is recommended, discouraging upfront biopsy or resection. Surgery is performed at either 6 or 12 weeks after neoadjuvant chemotherapy based on response, considering that continuing beyond 12 weeks usually does not yield additional tumor shrinkage. Preservation of renal function is prioritized, favoring NSS with either bilateral partial nephrectomies or total nephrectomy and contralateral partial nephrectomy. At week 6 of VAD, based on response, patients may undergo no surgery, bilateral partial

nephrectomies, or continue with VAD for a total of 12 weeks if tumors are unresectable. If less than a partial response at week 6, renal biopsies in both kidneys are recommended to determine histology before continuing with VAD. After confirming FHWT, staging and histology guide further therapy. Molecular biomarkers are not studied in this setting. Patients switch to EE4A, DD4A, or regimen I based on risk assessment. RT is often administered 10 to 14 days after surgery, considering the patient's age and other factors. Local stage III, regardless of metastases, determines the need for flank RT or WAI. Upfront biopsy does not upstage a tumor to stage III for determining RT. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting, and patients with a complete response at 6 weeks do not require RT.

Neoadjuvant therapy using the VAD regimen is recommended for children with metastatic bilateral renal tumors, irrespective of a predisposing condition. Upfront biopsy or resection is discouraged, and the decision for surgery at either 6 or 12 weeks is based on the response to chemotherapy, with NSS recommended when feasible. Post-chemotherapy, patients are stratified based on histology (blastemal predominant), and treatment is tailored accordingly. Regimen DD4A or regimen I is chosen, with DD4A for those without blastemal predominant histology or complete response at 6 weeks, and augmented therapy with regimen I for those with blastemal predominant histology. Molecular biomarkers' use in this context hasn't been studied. Radiation therapy, including flank RT or WAI, is considered based on local stage III criteria, and whole lung irradiation may be administered for lung metastases and extrapulmonary sites requiring radiation. Patients with a complete response at 6 weeks post-chemotherapy might not need radiation.

Treatment regimens used for Wilms tumor (AREN0533 study)[31]:



Regimen DD4A

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	16	19	22	25
	A			D			A			D			A	D*	A	D*	A
	V	V	V	V	V	V	V	V	V	V			V*	V*	V*	V*	V*
	RT																

Regimen M

Week	1 through 6	7	8	9	10	11	12	13	16	19	22	25	28	31
	Regimen	C			C					C		C		
	DD4A	E			E					E		E		
			V	V		V	V	V*	V*		V*		V*	V*
								A*	A*		A*		A*	A*
								D*	D*		D*		D*	D*
		RT												

V: vincristine: 0.025 mg/kg/dose intravenously (IV) × 1 for infants < 1 year; 0.05 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 1.5 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg).

V(*): vincristine: 0.034 mg/kg/dose IV × 1 for infants < 1 year; 0.067 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 2 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg).

A: dactinomycin 0.023 mg/kg/dose IV × 1 for infants < 1 year; 0.045 mg/kg/dose IV × 1 for children ≥ 1 year (maximum dose: 2.3 mg).

D: doxorubicin 1.5 mg/kg/dose IV × 1 for infants < 1 year; 45 mg/m^2/dose IV × 1 for children ≥ 1 year.

D(*): doxorubicin 1 mg/kg/dose IV × 1 for infants < 1 year; 30 mg/m^2/dose IV × 1 for children ≥ 1 year.

C: cyclophosphamide 14.7 mg/kg/dose IV × 5 days for infants < 1 year; 440 mg/m^2/dose IV × 5 days for children ≥ 1 year.

E: etoposide 3.3 mg/kg/dose IV × 5 days for infants < 1 year; 100 mg/m^2/dose IV × 5 days for children ≥ 1 year.

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs to delist due to withdrawal from the market among others and the fourth tackles other drugs approved by FDA/EMA but not yet approved by SFDA.

2.1 Additions

The following drugs has been newly approved for RCC and is SFDA registered. The first section below tackles the SFDA registered new molecule along with the HTA analysis and the section 2.4 includes drugs newly approved by FDA/EMA but are not SFDA-registered.

2.1.1 Avelumab

The following table describes the characteristics of Avelumab[32]:

Table 24. Avelumab Drug Information

Scientific Name Avelumab	
SFDA Classification	Prescription
SFDA approved Indication	Yes
US FDA	Yes
EMEA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	C64
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-class	Immune Checkpoint Inhibitor (PDL-1 Inhibitor)
ATC Code	L01XC32
Pharmacological Class (ASHP)	Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous

Dose (Adult) [DDD]*	800 mg once every 2 weeks (in combination with axitinib) until disease progression or unacceptable toxicity.
Maximum Daily Dose Adults*	800 mg once every 2 weeks
Dose (Pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose. - Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation* ● Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.

	- AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. ● Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently.
Prescribing edits*	CU, MD, PE, QL, ST
AGE (Age Edit)	For use in children ≥ 12 years of age, adolescents, and adults.
CU (Concurrent Use)	Used in combination with axitinib.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Needs to be prescribed by a medical oncologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum of 800 mg/dose every 2 weeks.
ST (Step Therapy)	• Avelumab is used in the treatment of advanced renal cell carcinoma (RCC). • It may be prescribed in certain situations, often in the second-line or later lines of therapy for advanced or metastatic RCC.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Used as part of a chemotherapy protocol.
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash,

	vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis, pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis.
Drug Interactions*	- Risk X: Thalidomide (Enhanced toxicity of thalidomide). - Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib,

	Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of Renal Cell Carcinoma treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Avelumab.**

Table 25. Avelumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Avelumab	HAS[11]	**May 18, 2020: Favorable opinion** for reimbursement of BAVENCIO (avelumab) in combination with axitinib in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.
	NICE[14]	**September 2, 2020: Negative recommendation:** Avelumab plus axitinib has the potential to be cost effective, but more evidence is needed: • Longer-term follow up of patients in JAVELIN Renal 101 would help to address the uncertainties about how long people live, and how long they live without their disease getting worse. • The economic model should reflect the treatment patients in the NHS would have after avelumab plus axitinib. Therefore, avelumab plus axitinib is **recommended through the Cancer Drugs Fund** while further data are collected, and the economic model is updated. The committee concluded that avelumab plus axitinib cannot be recommended for routine use.
	CADTH	N/A
	IQWIG[12]	**February 27, 2020: Positive recommendation** Avelumab is approved for several indications. This benefit assessment relates exclusively to the following area of application: Avelumab in combination with axitinib is used as first-line therapy in adult patients with advanced renal cell carcinoma (RCC).

	PBAC[13]	**March 2021: Positive recommendation** The PBAC recommended the listing of avelumab in combination with axitinib (AVE + AXI), for the first-line treatment of Stage IV clear cell variant RCC in patients classified as intermediate or poor according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of AVE + AXI would be acceptable if it were cost-minimized to nivolumab in combination with ipilimumab (NIVO + IPI). The PBAC considered that the totality of clinical evidence supported a benefit for AVE+AXI compared to sunitinib and noninferiority compared to NIVO + IPI. The PBAC considered there is a modest clinical need for an alternative treatment for RCC, and that AVE + AXI may benefit patients who may not be suitable for NIVO + IPI.

Conclusion Statement – Avelumab

Avelumab is used for the treatment of advanced renal cell carcinoma (in combination with axitinib). It is used for the second-line or later lines of therapy for advanced or metastatic RCC. The use of Avelumab is backed by some HTA bodies as HAS, PBAC, and IQWIG with positive recommendations. However, it has a negative recommendation by NICE for use in RCC. Severe side effects may limit the use of avelumab in some cases such as: Immune-Related Adverse Events, skin/infusion reactions and hematologic toxicities.

2.1.2 Belzutifan

The following table describes the characteristics of Belzutifan[33]:

Table 26. Belzutifan Drug Information

SCIENTIFIC NAME Belzutifan	
SFDA Classification	Prescription
SFDA	Off-label
US FDA	Yes
EMA	Off-label

MHRA	Yes
PMDA	Off-label
Indication (ICD-10)	C64
Drug Class	Antineoplastic Agent
Drug Sub-class	HIF-2ALPHA INHIBITOR
ATC Code	L01XX74
Pharmacological Class (ASHP)	Antineoplastic Agent
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	PO
Dose (Adult) [DDD]*	Oral: 120 mg once daily until disease progression or unacceptable toxicity
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Hepatic adjustment:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Adjustment for toxicity:** Recommended initial starting dose: 120 mg once daily First dose reduction: 80 mg once daily Second dose reduction: 40 mg once daily Third dose reduction: Permanently discontinue belzutifan
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit):	Not approved for use in pediatric patients.
CU (Concurrent Use Edit):	N/A

G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Needs to be prescribed by a medical oncologist.
PA (Prior Authorization):	Should be prescribed by a medical oncologist for the treatment of adult patients with von Hippel-Lindau (VHL)-associated RCC, or as a subsequent treatment option for relapsed/stage IV kidney cancer of clear cell histology in patients who are immune-oncology (IO) therapy naïve or have received prior IO therapy.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Useful in certain circumstances as a subsequent treatment option for relapsed/stage IV kidney cancer of clear cell histology in patients who are immune-oncology (IO) therapy naïve or have received prior IO therapy. Used for the management of von Hippel-Lindau (VHL)-associated RCC.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Fatigue, nausea and vomiting, anemia, decreased appetite, dizziness, or headache. **Most serious:** Hypertension, liver enzyme abnormalities, hemorrhagic events and thrombotic microangiopathy
Drug Interactions*	**Category X:** No drug interactions of Category X were found. **Category D**: Atogepant

Special Population	N/A
Pregnancy	Based on animal reproduction studies, in utero exposure to belzutifan may cause fetal harm. Embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations were observed when pregnant rats were administered belzutifan at doses resulting in maternal exposures ≥0.2 times the recommended human dose of 120 mg (based on AUC).
Lactation	It is not known if belzutifan is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last belzutifan dose.
Contraindications	There are no contraindications listed in the manufacturer's US labeling.
Monitoring Requirements	Monitor hemoglobin (prior to therapy initiation and periodically throughout treatment); closely monitor patients who are dual UGT2B17 and CYP2C19 poor metabolizers due to the potential increased incidence or severity of anemia. Monitor oxygen saturation (prior to therapy initiation and periodically throughout treatment). Evaluate pregnancy status in patients who may become pregnant. Monitor for signs/symptoms of anemia and hypoxia. Monitor adherence. The American Society of Clinical Oncology hepatitis B virus (HBV) screening and management provisional clinical opinion recommends HBV screening with hepatitis B surface

	antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up.
Precautions	N/A
Black Box Warning	Exposure to belzutifan during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of belzutifan. Advise patients of these risks and the need for effective nonhormonal contraception. Belzutifan can render some hormonal contraceptives ineffective.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Renal Cell Carcinoma treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Belzutifan.**

Table 27. Belzutifan HTA Recommendations

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Belzutifan	NICE	N/A
	CADTH[15]	**February 21, 2023: Conditional recommendation:** The CADTH pCODR Expert Review Committee (pERC) recommends that belzutifan be reimbursed for the treatment of adult patients with VHL disease who require therapy for associated nonmetastatic RCC, CNS

		hemangioblastomas, or nonmetastatic pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery only if the condition listed below are met: - Patients must have good performance status. - Adult patients with VHL disease who require therapy for associated nonmetastatic RCC, CNS hemangioblastomas, or nonmetastatic pNET, not requiring immediate surgery. - Belzutifan should be discontinued upon any of the following: Clinical or radiographic disease progression/Intolerance of therapy - Belzutifan should be initiated by specialists with expertise in the management of VHL diseaseassociated tumors. - Belzutifan should be administered as a monotherapy - A reduction in price - The feasibility of adoption of belzutifan must be addressed
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Belzutifan

Belzutifan is a medication used in the treatment of von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC). It is indicated for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), when the cancer does not require immediate surgery. The use of Belzutifan is backed by some HTA bodies as CADTH[15] with a conditional recommendation. Severe side effects may limit the use of belzutifan in some cases such as: Immune-Related Adverse Events, liver enzymes elevation and harm to developing fetus.

2.2 Modifications

The prescribing edit "MD" was added to all antineoplastic agents included in the drug summary spreadsheet: "to be prescribed by a medical oncologist". ICD-10 codes were adjusted to "C64 – malignant neoplasm of kidney, except renal pelvis".

In addition, the following modifications and adjustments have been implemented since the 2020 report:

Table 28. Prescribing Edits (PE) Modifications for Kidney Cancer Medications

Drugs	PE modifications
Axitinib	Add AGE: no approved for use in pediatric patients. Add PE: used as part of a chemotherapy protocol as monotherapy or in combination with pembrolizumab or avelumab.
Bevacizumab	Remove PA. Add ST: not a preferred treatment option; other contemporary therapies have replaced the use of bevacizumab in the treatment of renal cell carcinoma. Add PE: used as part of a chemotherapy protocol, as monotherapy or as part of a combination regimen.
Cabozantinib	Add AGE: for use in children ≥ 12 years of age, adolescents, and adults. Add PE: used as part of a chemotherapy protocol, as monotherapy or as part of a combination regimen. Modify PA: should be prescribed by a medical oncologist for the treatment of RCC in adult patients, as part of chemotherapy protocol either as monotherapy or as part of a combination regimen, in patients with advanced RCC.
Carboplatin (RCC)	Add CU: carboplatin should be used in combination with paclitaxel or gemcitabine. Used in combination with anti-emetic agents. Add PE: used per protocols mentioned regarding combination options and sequence of therapy. Add ST: carboplatin is typically not considered a first-line treatment for RCC; considered in later lines of therapy.
Carboplatin (Wilms tumor)	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy.

	Add ST: recommended for relapsed/refractory disease.
Cisplatin	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: cisplatin is not typically considered a first-line treatment for renal cell carcinoma (RCC). Considered in later lines of therapy
Cyclophosphamide	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add QL: for IV: some experts recommend no exceeding 1000mg/dose. For oral: 150 mg/day. Add ST: not usually the first-line treatment.
Doxorubicin	Remove PA. Add QL: cumulative lifetime limit: 400 mg/m^2 Add PE: part of a chemotherapy treatment protocol
Erlotinib	Remove PA. Add ST: not a standard first-line treatment for RCC. Considered in later lines of therapy, particularly in patients with advanced or metastatic RCC who have failed previous treatments. Add AGE: not approved for use in pediatric patients.
Etoposide	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: recommended for relapsed/refractory disease.
Everolimus	Remove PA. Add PE: used as part of a treatment protocol (most commonly in combination with Lenvatinib); can be used as monotherapy.
Gemcitabine	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: gemcitabine is not typically considered a first-line treatment for renal cell carcinoma (RCC). considered in later lines of therapy.
Ipilumab	Add CU: ipilimumab should be used in combination with nivolumab.

	Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add PA: ipilimumab should be prescribed by a medical oncologist in combination with nivolumab (for a maximum of 4 combination doses) as first-line treatment in patients with poor/intermediate risk stage IV RCC, or as second-line treatment in patients with favorable risk stage IV RCC. Add QL: administer for a maximum of 4 combination doses (ipilimumab + nivolumab); followed by nivolumab monotherapy.
Lenvatinib	Remove PA, ST. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy.
Mesna	Add PE: used as part of a chemotherapeutic protocol.
Nivolumab	Remove PA. Add PE: used as part of a chemotherapy protocol, either as monotherapy or in combination with ipilimumab or Cabozantinib.
Paclitaxel	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy. Add ST: Paclitaxel is not typically considered a first-line treatment for renal cell carcinoma. Considered in later lines of therapy.
Pazopanib hydrochloride	Remove PA. Add AGE: not approved for use in pediatric patients. Add ST: used as a 2nd line option in patients with stage IV disease.
Pembrolizumab	Add PE: used per protocols combination options either ad monotherapy or in combination with axitinib or lenvatinib & sequence of therapy.
Sorafenib	Remove PA. Add ST: used as a 3rd line option in recurrent RCC post nephrectomy. Add AGE: not approved for use in pediatric patients.
Sunitinib	Remove PA. Add AGE: not approved for use in pediatric patients.
Vincristine	Remove PA. Add PE: used per protocols mentioned above regarding combination options & sequence of therapy.

2.3 Delisting

The medication below is not SFDA registered[34], therefore, it is recommended to delist the following drug from CHI formulary:

- Ranitidine

In addition, drugs related to supportive care that are not specific for the management of RCC were delisted from the drug summary spreadsheet: alendronic acid, chlorpheniramine, denosumab, dexamethasone, loperamide, magnesium sulfate, paracetamol, potassium chloride, prednisone, TMP/SMX, zoledronic acid.

2.4 Other Drugs

The drug detailed in this section is a supplement commonly used for RCC, however, **these drugs are not registered by the SFDA**.

2.4.1 Dactinomycin

Dactinomycin (COSMEGEN®) was approved by the FDA in 1964. It is an actinomycin indicated for the treatment of adult and pediatric patients with Wilms tumor, as part of a multi-phase, combination chemotherapy regimen. For Wilms Tumor, the recommended dose is 45 mcg/kg intravenously once every 3 to 6 weeks for up to 26 weeks, as part of a multi-agent combination chemotherapy regimen. Special warnings associated with this medication include cardiotoxicity, hepatotoxicity, and increased risk of secondary malignancies[35]. Dactinomycin is **essential** in the treatment of Wilms tumors in pediatric patients and will be included in the drug summary spreadsheet as a non-registered drug.

2.4.2 Savolitinib

Savolitinib (Orpathys®) is a potent antineoplastic agent. Targeting intracellular cMET with cMET kinase inhibitors represents another approach for HGF-cMET signaling pathway deactivation. It is formulated as tablets for the oral route of administration. It is under development for usage in clear cell renal cell carcinoma. For its dosage, In clinical trials it was dosed as 600 mg or 400 mg savolitinib once daily in 21-day cycles. Its most common side effects are peripheral edema, Nausea, vomiting, increased ALT and AST, hypoalbuminuria and decreased appetite[36].

2.4.3 Temsirolimus

Temsirolimus (Torisel®) was approved by the FDA and EMA in 2007. It is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. The recommended dose is 25 mg infused over a 30–60-minute period once a week. Treat

until disease progression or unacceptable toxicity. Antihistamine pre-treatment is recommended, and dose reduction is required in patients with mild hepatic impairment. Hypersensitivity/Infusion Reactions (including some life-threatening and rare fatal reactions) can occur early in the first infusion: patients should be monitored throughout the infusion. Use with caution when treating patients with mild hepatic impairment and reduce dose[37].

2.4.4 Tivozanib

Tivozanib (Fotivda®) was approved by the FDA on March 10, 2021, and by the EMA on August 24, 2017. It is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies. It is recommended to be given 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity. Special warnings associated with this medication include cardiac toxicity, hemorrhagic events and VTE[38].

Section 3.0 Key Recommendations Synthesis

Surgical management

- Consider nephron-sparing surgery (partial nephrectomy) for specific patient groups, including:
    - Unilateral stage I–III tumors when technically feasible
    - Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
    - Patients at a relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (e.g., hypertension, diabetes, nephrolithiasis)
    - In cases where partial nephrectomy is not possible, a radical nephrectomy is considered and should be determined by tumor size, location, and the overall health of the patient[16-17].
- For potentially surgically resectable tumor: consider tissue sampling and primary treatment with
    - Cytoreductive nephrectomy in select patients

      or
    - Systemic therapy (preferred in clear cell histology with poor-risk features)
- For surgically unresectable tumor: consider systemic therapy[16].
- For potentially surgically resectable tumor: Potentially resectable primary tumors with solitary metastasis or multiple resectable lung metastases: these patients should undergo primary nephrectomy and resection of the metastatic lesion/s[17].
- Following complete resection, no further therapy or “adjuvant therapy” is indicated[17].

Potentially resectable primary and multiple non-resectable metastases: these patients should undergo resection of the primary tumor if in good performance status, then start systemic therapy:

- Clear cell histology with good or intermediate risk: options of therapy include systemic therapy with either sunitinib, bevacizumab and interferon α 2a, or pazopanib.
- High-dose interleukin-2 may be used in highly selected patients and centers.

- Clear cell histology with poor risk: temsirolimus is the preferred treatment. An alternative option is sunitinib.
- Non-clear cell histology: options of therapy include temsirolimus, sunitinib, or sorafenib. Medullary and collecting duct carcinomas should be treated with platinum-based chemotherapy[17].

Stage IV kidney cancer: Clear cell histology: treated with

- Clinical trial

  or

- first line therapies for **favorable risk:**
  - Axitinib + pembrolizumab
  - Cabozantinib + nivolumab
  - Lenvatinib + pembrolizumab

  or

- first line therapies for **poor/intermediate risk:**
  - Axitinib + pembrolizumab
  - Cabozantinib + nivolumab
  - Ipilimumab + nivolumab
  - Lenvatinib + pembrolizumab

    It is worth noting that this combination remains superior to sunitinib on clinical outcomes as first-line treatment for advanced renal cell carcinoma as observed by the CLEAR trial[19].
  - Cabozantinib

  or

- Metastasectomy

  or

- stereotactic body radiation therapy (SBRT)

  or

- ablative techniques for oligometastatic disease

  or

- Metastasectomy with complete resection of disease, followed by adjuvant pembrolizumab within 1 year of nephrectomy

and

- Best supportive care: include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases (offered for patients only if not fit for systemic treatment)[16].

Stage IV kidney cancer: Non-clear cell histology: treated with:

- Clinical trial or cabozantinib (preferred)

  Or

- Lenvatinib+ pembrolizumab is suggested as first-line treatment for patients with non-clear cell RCC, regardless of histology, based on results from the Keynote B-61 trial.

  Or

- Systemic Therapy:
  - Lenvatinib + everolimus
  - Nivolumab
  - Nivolumab + cabozantinib
  - Pembrolizumab
  - Sunitinib

  or

- Metastasectomy

  or

- SBRT

  or

- ablative techniques for oligometastatic disease

  and

- Best supportive care[16].

Active surveillance is a viable option for the initial management of patients with clinical stage T1 renal lesions, including:

- Small renal masses <3 cm, given the high rates of benign tumors and low metastatic potential.

- Active surveillance is recommended for patients with T1a tumors (≤4 cm) that have a predominantly cystic component.
- Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention[16].

Management of local/locoregional disease

Systemic treatment for clear cell renal cell carcinoma

- The combination of PA should be considered as a front-line therapeutic option for patients with advanced disease, irrespective of IMDC prognostic subgroups and PD-L1 biomarker status while the combination of IN should be considered as a first-line option in patients with IMDC intermediate- and poor-risk disease.
- VEGF-targeted therapy is recommended in those patients where pembrolizumab/axitinib or ipilimumab/nivolumab are not available or are contraindicated[21–24].

Adjuvant therapy in clear cell renal cell carcinoma

- For patients at intermediate or high risk operable clear cell RCC (ccRCC), adjuvant Pembrolizumab could be considered as an option after careful patient counselling regarding immature Overall survival (OS) and potential long-term adverse events. Treatment initiation should occur within 12 weeks post-surgery and continue for up to 1 year[21–24].
- Patients who have undergone complete resection of their oligometastatic disease could be offered adjuvant pembrolizumab[21–24].
- Strongly discourage the use of adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib[18].

Management of metastatic disease

- Cytoreductive nephrectomy may be offered to select patients with metastatic ccRCC[26,27].
- Strongly advise against performing cytoreductive nephrectomy (CN) in MSKCC poor-risk patients[18].
- Do not offer chemotherapy to patients with metastatic renal cell carcinoma[18].

First-line treatment for advanced ccRCC

- Lenvatinib–pembrolizumab has gained FDA approval but not EMA approval. It's now included among other combinations targeting VEGFR and PD-1 inhibitors (such as axitinib–pembrolizumab or cabozantinib–nivolumab

recommended as initial treatment for advanced ccRCC, regardless of IMDC risk groups. No specific preference is indicated among VEGFR TKI–PD-1 inhibitor combinations[21–24].

- **Single agent targeted therapy:** Strongly recommend offering nivolumab or cabozantinib for immune checkpoint inhibitor-naive, vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy[18].
- Ipilimumab–nivolumab remains the recommended first-line treatment for IMDC intermediate- and poor-risk disease[21–24, 26,27].
- Patients with favorable-risk disease requiring systemic therapy may be offered an ICI in combination with a VEGFR TKI[26,27].
- Sunitinib, pazopanib and tivozanib are options if immunotherapy is not suitable or available for first-line combinations[21–24].
- Cabozantinib is also an alternative for IMDC intermediate- and poor-risk disease in patients unable to receive first-line PD-1 inhibitor-based therapy[21–24].
- In the first-line setting, only ICI-based combinations that demonstrate a survival advantage are recommended. Axitinib–avelumab and bevacizumab–atezolizumab, as they don't show an OS advantage, are not recommended[21–24].
- Lenvatinib–everolimus is not considered a standard initial treatment for metastatic disease. It can be recommended as subsequent therapy after the initial treatment alongside other agents[21–24].
- The use of high-dose interleukin-2 (HD-IL2) may be considered in the first-line systemic therapy setting for patients with metastatic ccRCC. Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful[26,27].
- It is strongly advised against administering IpiNivoCabo treatment to patients with metastatic clear cell renal cell carcinoma (ccRCC). Individuals expressing interest in triplet therapy are encouraged to participate in a clinical trial[26,27].

Second- or later-line systemic treatment for ccRCC

- Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone[18,26,27].
- Patients progressing on combination immunotherapy (e.g., nivolumab and ipilimumab) should be offered a VEGFR TKI[26,27].
- Patients who progress after initial therapy combining VEGFR TKI with an ICI may be offered an alternate VEGFR TKI as a single agent[26,27].

- On December 14, 2023, the FDA approved belzutifan for patients with advanced renal cell carcinoma (RCC) following PD-1 or PD-L1 inhibitor and a VEGF-TKI[28,29].

Medical treatment for advanced/metastatic non-clear-cell RCC

- Cabozantinib is the recommended initial treatment for advanced papillary RCC without further molecular testing.
- Other choices include sunitinib, pembrolizumab without additional molecular testing, and savolitinib (if accessible) for tumors driven by MET alterations[21–24].
- **Targeted therapy in non-clear-cell RCC**: Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC[18].

Wilms Tumor

- For most children with suspected WT, surgery is recommended, even for those initially considered unresectable or with bilateral or metastatic disease. Risk assessment helps determine the need for and type of adjuvant therapy after surgery. Unilateral nephrectomy is often performed upfront for children with resectable unilateral kidney disease[30].

Surgery

- Most patients with favorable histology WT undergo unilateral radical ureteronephrectomy, while nephron-sparing surgery (NSS) is reserved for bilateral disease, genetically predisposed individuals, or those at higher risk for renal failure[30].
- NSS is not recommended for unilateral disease without genetic predisposition[30].

Chemotherapy

- Chemotherapy is proven to enhance the survival of most children with Wilms tumor (WT) when combined with surgery, with or without radiotherapy[30].
- Various chemotherapy regimens, such as EE4A, DD4A, VAD, regimen M, and regimen I, are employed[30].
- Although some agents overlap, the schedules differ, and certain regimens serve for neoadjuvant or adjuvant purposes[30].

Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy regimens are employed for patients who cannot undergo upfront nephrectomy. Options include EE4A, DD4A, or VAD[30].

Adjuvant Chemotherapy

- Regimens for adjuvant chemotherapy encompass: EE4A, DD4A, regimen M, and regimen I[30].
- The specific regimens employed depend on the context and risk stratification[30].

Radiation Therapy

- Adjuvant RT is recommended for higher-risk patients post-surgery but is not indicated for those with low-stage, lower-risk disease[30].
- NCCN Panel suggests starting RT by day 10 after surgery but no later than day 14[30].
- Coordination between RT and chemotherapy is essential to avoid concurrent administration of full doses of dactinomycin or doxorubicin with RT allowing for the administration of these agents at full doses before the initiation of RT[30].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Renal Cell Carcinoma report** and aims to provide recommendations to aid in the management of Renal Cell Carcinoma. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Renal Cell Carcinoma. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Renal Cell Carcinoma Scope

Section	Rationale/Updates
Section 1.1 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Renal Cell Carcinoma (2020-2021) [21–24]	**Management of local/locoregional disease** **Systemic treatment for clear cell renal cell carcinoma** • The combination of PA should be considered as a front-line therapeutic option for patients with advanced disease, irrespective of IMDC prognostic subgroups and PD-L1 biomarker status [I, A], while the combination of IN should be considered as a first-line option in patients with IMDC intermediate- and poor-risk disease [I, A]. • VEGF-targeted therapy is recommended in those patients where pembrolizumab/axitinib or ipilimumab/nivolumab are not available or are contraindicated [I, A–II, B]. • There is limited data for treatment after progression or intolerance on PA or IN. VEGF TKIs are the recommended treatment for these patients [III, B]. **Adjuvant therapy in clear cell renal cell carcinoma** • For patients at intermediate or high risk operable clear cell RCC (ccRCC) (as defined by the study). Adjuvant Pembrolizumab could be considered as an option after careful patient counselling regarding immature Overall survival (OS) and potential long-term adverse events [I,C]. Treatment initiation should occur within 12 weeks post-surgery and continue for up to 1 year. • In the case of the M1 NED population, for patients who experience a relapse within a year of nephrectomy, the established treatment involves using programmed cell death protein 1 (PD-1)-based combination therapy [I, A]. Considering metastasectomy as an alternative to this systemic therapy for patients with synchronous or early oligometastatic disease is generally not recommended [I, D] and requires a decision from a multidisciplinary team. • Patients who have undergone complete resection of their oligometastatic disease could

	be offered adjuvant pembrolizumab [II, B]. • However, offering incomplete resection to patients with oligometastatic disease is not advisable [III, D]. **Management of metastatic disease** **First-line treatment for advanced ccRCC** • Lenvatinib–pembrolizumab [I, A] has gained FDA approval but not EMA approval. It's now included among other combinations targeting VEGFR and PD-1 inhibitors (such as axitinib–pembrolizumab [I, A] or cabozantinib–nivolumab [I, A] recommended as initial treatment for advanced ccRCC, regardless of IMDC risk groups. No specific preference is indicated among VEGFR TKI–PD-1 inhibitor combinations and comparing across different trials indirectly is discouraged [I, D]. • Ipilimumab–nivolumab remains the recommended first-line treatment for IMDC intermediate- and poor-risk disease [I, A]. • Immunotherapy-based treatment shows notable effectiveness in sarcomatoid renal tumors and is strongly recommended over using a single-agent VEGFR TKI [II, A]. • Sunitinib [I, A], pazopanib [I, A], and tivozanib [II, B] are options if immunotherapy is not suitable or available for first-line combinations. Cabozantinib [II, A] is also an alternative for IMDC intermediate- and poor-risk disease in patients unable to receive first-line PD-1 inhibitor-based therapy. • In IMDC favorable-risk disease, sunitinib or pazopanib could be considered alternatives to PD-1 inhibitor-based combination therapy due to the lack of clear superiority of PD-1-based combinations over sunitinib in this patient subgroup [I, B]. • Surveillance might be an option for a small group of patients but needs careful consideration [III, C]. • In the first-line setting, only ICI-based combinations that demonstrate a survival advantage are recommended. Axitinib–avelumab and bevacizumab–atezolizumab, as they don't show an OS advantage, are not recommended [I, D].

	• Discontinuing ICIs should be considered after two years of therapy [IV, C]. • Lenvatinib–everolimus is not considered a standard initial treatment for metastatic disease [I, D], but it can be recommended as subsequent therapy after the initial treatment alongside other agents [III, B]. **After disease progression on PD-1 inhibitor-based combination therapy for ccRCC** • Continuing treatment with a VEGFR TKI after initial PD-1 inhibitor-based therapy shows moderate response rates and is suggested as the usual practice [III, B]. However, these findings come from less than ideal studies. The selected VEGFR-targeted medication should be one they haven't used before [III, B]. • There isn't enough randomized evidence to back the continuation of immune checkpoint inhibitors after progression from initial therapy, so this approach is not advised [IV, D]. **Medical treatment for advanced/metastatic papillary RCC** • Cabozantinib is the recommended initial treatment for advanced papillary RCC without further molecular testing [II, B]. Other choices include sunitinib [II, B], pembrolizumab [III, B] without additional molecular testing, and savolitinib (if accessible) for tumors driven by MET alterations [III, C]. • In the second-line, priority should be given to medications not previously administered in the first-line treatment [IV, C]. In some cases where systemic therapy lacks substantial data, selected patients may consider best supportive care [IV, C]. **New therapies/indications in renal cell carcinoma:** • For Advanced RCC after prior VEGF-targeted therapy: Cabozantinib can be used. • Cabozantinib plus nivolumab are considered as first-line treatment of advanced RCC. • For Advanced or metastatic RCC following one prior VEGF-targeted therapy: Lenvatinib plus everolimus is considered. • Lenvatinib plus pembrolizumab are considered as first-line treatment of advanced RCC • For Treatment of advanced RCC after failure of one or two regimens of antiangiogenic

	therapy, recommend Nivolumab. • Nivolumab plus ipilimumab are used for first-line treatment of intermediate-/ poor-risk advanced RCC. • Pembrolizumab plus axitinib are used for first-line treatment of advanced clear cell RCC • Tivozanib is used as first targeted therapy in recurrent or metastatic RCC with a clear cell component.
Section 1.2 National Comprehensive Care Network (NCCN) Kidney Cancer (v1.2024) [16]	The first-line treatment options for stage I, II, and III kidney cancer typically include surgical interventions, such as: **Nephrectomy** which is the surgical removal of the affected kidney is the primary treatment for localized renal cancer. This may involve removing only the tumor (partial nephrectomy) or the entire kidney (radical nephrectomy). • **Partial Nephrectomy (PN):** This approach is preferred when feasible, especially for smaller tumors or cases where preserving kidney function is crucial. It involves removing only the tumor, leaving the rest of the kidney intact. • **Radical Nephrectomy (RN):** In cases where partial nephrectomy is not possible, a radical nephrectomy involves removing the entire kidney along with surrounding tissues and lymph nodes. • The choice between partial and radical nephrectomy depends on factors such as tumor size, location, and the overall health of the patient **General principles of management for renal cell carcinoma:** • Consider nephron-sparing surgery (partial nephrectomy) for specific patient groups, including: o Unilateral stage I–III tumors when technically feasible o Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer o Patients at a relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (e.g., hypertension, diabetes, nephrolithiasis) • Radical and partial nephrectomies can be performed using open, laparoscopic, or

	robotic surgical techniques.
	• Optional regional lymph node dissection is recommended for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at the time of surgery.
	• Adrenalectomy may be omitted if the adrenal gland is uninvolved.
	• Specialized teams or referral to high-volume centers may be necessary for cases with extensive inferior vena cava involvement.
	• Thermal ablation methods (e.g., cryosurgery, radiofrequency ablation, microwave ablation) are viable options for managing clinical stage T1 renal lesions.
	  • Thermal ablation is a consideration for clinical T1b masses in select patients ineligible for surgery.
	  • Biopsy of lesions is recommended before or during ablation.
	  • Ablative techniques may require multiple treatments to achieve comparable local oncologic outcomes to conventional surgery.
	o Stereotactic body radiation therapy (SBRT) is viewed as an ablative therapy and may be considered for medically inoperable patients (not optimal surgical candidates) with stage I (category 2B), II, or III (both category 3) kidney cancer.
	o Active surveillance is a viable option for the initial management of patients with clinical stage T1 renal lesions, including:
	• Small renal masses <3 cm, given the high rates of benign tumors and low metastatic potential.
	• Active surveillance is recommended for patients with T1a tumors (≤4 cm) that have a predominantly cystic component.
	• Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
	• Active surveillance involves serial abdominal imaging with timely intervention if the mass shows changes indicative of increasing metastatic potential.

- Periodic metastatic surveys, including blood work and chest imaging, are recommended during active surveillance.
- Generally, patients suitable for cytoreductive nephrectomy before systemic therapy should have:
  - Excellent performance status (ECOG PS <2)
  - No brain metastasis
- Patients with large-volume distant metastases or tumors with substantial sarcomatoid burdens should receive systemic therapy before cytoreductive nephrectomy.

Kidney Cancer management according to the staging of the disease

Stage I (T1a) kidney cancer management	
Partial nephrectomy **(preferred)** Or Ablative techniques Or Active surveillance Or Radical nephrectomy (in select patients)	**Adjuvant treatment:** Surveillance
Stage I (T1b) kidney cancer management	
Partial nephrectomy Or Radical nephrectomy Or Active surveillance (in select patients) Or Ablative techniques (in select patients)	**Adjuvant treatment:** Surveillance
Stage II kidney cancer management	

	Partial nephrectomy Or Radical nephrectomy	**Adjuvant treatment:** Adjuvant pembrolizumab (grade 4 tumors with clear cell histology +/- sarcomatoid features) Or Surveillance
	Stage III kidney cancer management	
	Radical nephrectomy Or Partial nephrectomy, if clinically indicated	**Adjuvant treatment:** *Clear cell histology:* Adjuvant pembrolizumab or Surveillance or Adjuvant sunitinib (category 3) *Non-clear cell histology:* Surveillance or Clinical trial
	Stage IV kidney cancer management	
	For potentially surgically resectable tumor: consider tissue sampling and primary treatment with • Cytoreductive nephrectomy in select patients Or • **Systemic therapy** (preferred in clear cell histology with poor-risk	For surgically unresectable tumor: consider **systemic therapy** (will be discussed below)

	features)	

For stage IV kidney cancer or relapsing disease, tissue sampling may yield the following:

3. **Clear cell histology:** treated with

- Clinical trial

or

- first line therapies

or

- Metastasectomy

or

- stereotactic body radiation therapy (SBRT)

or

- ablative techniques for oligometastatic disease

or

- Metastasectomy with complete resection of disease, followed by adjuvant pembrolizumab within 1 year of nephrectomy

and

- Best supportive care: include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases.

4. **Non-clear cell histology:** treated with:

- Clinical trial (preferred)

  or
- Systemic Therapy (KID-C, 2 of 2)

  or
- Metastasectomy

  or

- SBRT
  or
- ablative techniques for oligometastatic disease
  and
- Best supportive care

First line treatment options for relapse/stage IV kidney cancer (clear cell histology)

First line therapy for clear cell histology			
Risk	**Preferred regimens**	**Other recommended regimens**	**Useful in certain circumstances**
Favorable	· Axitinib + pembrolizumab (category 1) · Cabozantinib + nivolumab (category 1) · Lenvatinib + pembrolizumab (category 1)	· Axitinib + avelumab · Cabozantini (category 2B) · Ipilimumab + nivolumab · Pazopanib · Sunitinib	· Active surveillance · Axitinib (category 2B) · High-dose IL-2d (category 2B)
Poor/ intermediate	· Axitinib + pembrolizumab (category 1) · Cabozantinib + nivolumab (category 1) · Ipilimumab + nivolumab (category 1) · Lenvatinib + pembrolizumab	· Axitinib + avelumab · Pazopanib · Sunitinib	· Axitinib (category 2B) · High-dose IL-2 for patients with excellent performance status and normal organ

	(category 1) • Cabozantinib		function (category 3) • Temsirolimus (category 3)

Subsequent treatment options for relapse/stage IV kidney cancer (clear cell histology)

Subsequent therapy for clear cell histology (in alphabetical order by category)			
Immuno-oncology (IO) Therapy History Status	**Preferred regimens**	**Other recommended regimens**	**Useful in certain circumstances**
IO Therapy Naïve	None	• Axitinib + pembrolizumab • Cabozantinib • Cabozantinib + nivolumab • Ipilimumab + nivolumab • Lenvatinib + everolimus • Lenvatinib + pembrolizumab • Nivolumab	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib (For patients who received ≥2 prior systemic therapies) • Belzutifan (category 2B) • Bevacizumab (category 2B) (An FDA-approved biosimilar is an appropriate substitute for bevacizumab) • High-dose IL-2 for selected patients (Patients with excellent performance status and normal organ function) (category 2B) • Temsirolimus (category 2B) • Axitinib + avelumab (category 3)

Prior IO Therapy	None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib	• Axitinib + pembrolizumab • Cabozantinib + nivolumab • Everolimus • Ipilimumab + nivolumab • Lenvatinib + pembrolizumab • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab (category 2B) (An FDA-approved biosimilar is an appropriate substitute for bevacizumab) • High-dose IL-2 for selected patients (Patients with excellent performance status and normal organ function) (category 2B) • Temsirolimus (category 2B) • Axitinib + avelumab (category 3)

Systemic therapy options for relapse/stage IV kidney cancer (non-clear cell histology)

Systemic therapy for non-clear cell histology		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Clinical trial • Cabozantinib	• Lenvatinib + everolimus • Nivolumab • Nivolumab + cabozantinib • Pembrolizumab • Sunitinib	• Axitinib • Bevacizumab* • Bevacizumab* + erlotinib for selected patients with advanced

			papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Bevacizumab* + everolimus • Erlotinib • Everolimus • Nivolumab + ipilimumab (category 2B) • Pazopanib • Temsirolimus (category 1 for poor-prognosis risk group; category 2A for other risk groups)
	*: An FDA-approved biosimilar is an appropriate substitute for bevacizumab		
	HEREDITARY RENAL CELL CARCINOMA: • Preoperative caution: Individuals suspected or diagnosed with PGL/PCC or VHL face an elevated risk of PCCs and should undergo blood and/or urine screening before any surgical procedure. • **BAP1-TPDS:** Surgical management guidelines for this syndrome are currently missing. • **BHDS:** For renal tumors, nephron-sparing surgery is the preferred treatment whenever feasible, acknowledging the potential for multiple tumors in an individual's lifetime. Ablative treatment options can be considered for those with substantial medical or surgical risks. • **HLRCC:** Due to the aggressive nature of tumors associated with HLRCC, surveillance is not recommended, and total radical nephrectomy should be considered.		

- **HPRC:** In cases of HPRC, nephron-sparing surgery is the preferred treatment for renal tumors when possible, considering the potential for multiple tumors in an individual's lifetime. Ablative treatment options can be considered for those with significant medical or surgical risks.
- **PGL/PCC:** Surgical resection is recommended for malignant tumors with non-aggressive histology and early stages, with partial nephrectomy as an option. For larger tumors or those with aggressive histology, such as high grade or sarcomatoid features, radical nephrectomy is recommended.
- **TSC:** Angiomyolipoma, a benign lesion associated with TSC, is managed separately. Nephron-sparing surgery is the preferred treatment for malignant renal tumors, with consideration for multiple tumors over an individual's lifetime. Ablative treatment options can be considered for those with significant medical or surgical risks.
- **VHL:** The management of localized renal masses in VHL patients typically follows the "3 cm rule." Intervention aims to balance the prevention of metastatic disease with the consideration of recurrent and multiple resections leading to chronic and progressive renal failure. Partial nephrectomy is recommended if possible, and referral to centers with expertise in complex partial nephrectomies and comprehensive care of VHL patients should be considered. Ablative treatment options can be considered for those with significant medical or surgical risks.

Kidney-specific systemic therapy for patients with confirmed hereditary RCC

Syndrome	Kidney-Specific Systemic Therapy
HLRCC	Useful in Certain Circumstances • Erlotinib plus bevacizumab[a,b]
TSC	Useful in Certain Circumstances • Everolimus[c]
VHL	Preferred Regimen • Belzutifan[d]

	Useful in Certain Circumstances • Pazopanib
	a An FDA-approved biosimilar is an appropriate substitute for bevacizumab b There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC. c Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter. d Belzutifan is FDA-approved for the treatment of VHL-associated RCC, central nervous system (CNS) hemangioblastomas, or pNET, not requiring immediate surgery.
Addition of a new section: Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for renal cell carcinoma (2017) [17]	**Localized disease (T1a)** • Surgical excision, preferably through partial nephrectomy (open, laparoscopic, or robotic), is the recommended treatment for all cases, particularly in patients with a solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency (EL 1). • Reserve radical nephrectomy (preferably laparoscopic) for cases where partial nephrectomy is technically infeasible after consultation with an experienced surgeon (EL 1). • Non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended, except for patients with significant comorbidities that prevent surgical intervention (EL 2). **Localized disease (T1b)** • The recommended treatment is radical nephrectomy (preferably laparoscopic) (EL 1). • Partial nephrectomy may be considered, especially in patients with a solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency. However, this should only be performed by an experienced surgeon in a high-volume center (EL 1). • Non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended. **Localized disease (T2)**

	• The recommended treatment is radical nephrectomy (EL 1). • Partial nephrectomy and non-surgical options (active surveillance, cryoablation, and radiofrequency ablation) are not recommended. **Localized disease (T3)** • The recommended treatment is radical nephrectomy with complete excision of all venous thrombus in the renal vein, inferior vena cava, and right atrium (EL 2). • These surgeries should only be performed in tertiary care centers with the availability of a cardiac, vascular, or hepatic surgeon, depending on the case (EL 2). **Excision of the ipsilateral adrenal gland** • Ipsilateral excision of the adrenal gland during radical nephrectomy is indicated in upper pole kidney tumors or the presence of a concurrent radiologically detectable adrenal gland lesion(s) (EL 2). **Lymph node dissection** • Resection of the regional lymph nodes (within Gerota's fascia) is an integral part of radical nephrectomy. • Resection of non-regional lymph nodes provides no therapeutic advantages but is used for staging purposes (EL 1). When performing partial nephrectomy, the surgeon should aim to obtain an adequate surgical margin and avoid tumor inoculation, except in patients with von Hippel–Lindau syndrome. **Metastatic advanced, unresectable disease** • For risk stratification of metastatic RCC, two valid options are available: i. The Memorial Sloan Kettering Cancer Center (MSKCC/Motzer) risk classification for metastatic disease ii. Heng Score for Metastatic RCC Prognosis.[39]. • Potentially resectable primary tumors with solitary metastasis or multiple resectable lung metastases: these patients should undergo primary nephrectomy and resection of the metastatic lesion/s (EL 2). Following complete resection, no further therapy or

	"adjuvant therapy" is indicated (EL 3). • Potentially resectable primary and multiple non-resectable metastases: these patients should undergo resection of the primary tumor if in good performance status (EL 1), then start systemic therapy according to the following guidelines: o Clear cell histology with good or intermediate risk: options of therapy include systemic therapy with either sunitinib (EL 1), bevacizumab and interferon α 2a, or pazopanib (EL 1). o High-dose interleukin-2 may be used in highly selected patients and centers. o Clear cell histology with poor risk: temsirolimus is the preferred treatment (EL 1). An alternative option is sunitinib (EL 2). o Non-clear cell histology: options of therapy include temsirolimus (EL 2), sunitinib (EL 2), or sorafenib (EL 2). Medullary and collecting duct carcinomas should be treated with platinum-based chemotherapy (EL 3). o Unresectable primary tumor with or without metastatic disease: These patients with good performance status should be offered systemic therapy according to their histological results and MSKCC risk group as in Item 4.9.3. • Recurrent disease post-primary nephrectomy: treatment will depend on whether resectable or not: o If resectable solitary metastasis: surgical resection should be attempted (EL 2). No systemic therapy is of benefit following complete resection (EL 3). o If non-resectable recurrence: the patient should be treated as metastatic disease according to their histological results, using the MSKCC Risk Score and/or Heng Score. • Second-line therapy post-tyrosine kinase inhibitor (TKI) failure: patients who fail with first-line TKIs should receive second-line therapy if in reasonable performance status. Options of second-line agents include nivolumab (EL 1), cabozantinib (EL 1), or axitinib (EL 1). In the absence of these options, everolimus can be considered. • Third-line therapy: consider everolimus (Level 3), sorafenib (Level 3), or clinical trials.

<table>
<tr><td></td><td>Metastatic renal cell carcinoma prognostic models
MSKCC risk classification
Prognostic criteria
Time from diagnosis to treatment <1 year Hemoglobin < lower limit of normal
Calcium >10 mg/dl (more than 2.5 mmol/L) Lactate dehydrogenase >1.5 x upper limit of normal Karnofsky performance status <80%
Risk stratification
favorable-risk group: No prognostic factors Intermediate risk: 1 or 2 prognostic factors Poor risk :3 prognostic factors
MSKCC: Memorial Sloan Kettering Cancer Center
Heng risk classification
Prognostic criteria
Time from diagnosis to systemic treatment <1 year Hemoglobin < lower limit of normal
Calcium >10 mg/dl (more than 2.5 mmol/L) Karnofsky performance <than 80% Neutrophil count > upper limit of normal Platelets count > upper limit of normal
Risk stratification
favorable-risk group : no prognostic factors Intermediate risk : 1 or 2 prognostic factors Poor risk: 3 or more prognostic factors</td></tr>
<tr><td>Addition of a new section:
American Society of Clinical Oncology (ASCO) Guideline on the Management of Metastatic Clear Cell Renal</td><td>Diagnosis
• For the diagnosis of metastatic ccRCC, it is recommended to compare tissue obtained from outside the primary disease site with the primary histology. The histologic evaluation should include common markers of ccRCC, such as paired box gene 8 and carbonic anhydrase IX (Evidence quality: High; Strength of recommendation: Strong).
• In selected circumstances, radiographic diagnosis of metastatic ccRCC may be employed. This is particularly applicable in settings where a previous diagnosis of renal cell carcinoma has been established, when biopsy of metastatic tissue is not readily</td></tr>
</table>

Carcinoma (2022-Rapid Recommendation Update (2023) [26,27]	accessible, or when RECIST 1.1 measurable disease is evident, especially within a year of the initial diagnosis (Evidence quality: Low; Strength of recommendation: Weak). **Role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma** • Cytoreductive nephrectomy may be offered to select patients with metastatic ccRCC (Evidence quality: High; Strength of recommendation: Strong). **Preferred options for first-line systemic treatment of metastatic clear cell renal cell carcinoma** • For select patients with metastatic ccRCC, an initial active surveillance strategy may be offered (Evidence quality: Moderate; Strength of recommendation: Strong). o Select patients include those with IMDC favorable and intermediate risk, patients with limited or no symptoms related to disease, a favorable histologic profile, a long interval between nephrectomy and the development of metastasis, or with a limited burden of metastatic disease. • All patients with metastatic ccRCC requiring systemic therapy in the first-line setting should undergo risk stratification into IMDC favorable (0), intermediate (1-2), and poor risk groups. Patients with intermediate- or poor-risk disease should be offered combination treatment with two immune checkpoint inhibitors (ICIs; i.e., ipilimumab and nivolumab) or an ICI in combination with a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI; Evidence quality: High; Strength of recommendation: Strong). • Patients with favorable-risk disease requiring systemic therapy may be offered an ICI in combination with a VEGFR TKI (Evidence quality: High; Strength of recommendation: Strong). • Select patients with metastatic ccRCC receiving systemic therapy in the first-line setting, including those with favorable-risk disease or with certain coexisting medical problems, may be offered monotherapy with either a VEGFR TKI or an ICI (Evidence quality: Moderate; Strength of recommendation: Strong). • The use of high-dose interleukin-2 (HD-IL2) may be considered in the first-line systemic

	therapy setting for patients with metastatic ccRCC. Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful (Evidence quality: Moderate; Strength of recommendation: Weak). o The significant toxicity of this regimen must be weighed in relation to the newer immunotherapy regimens that have largely replaced this treatment. The Expert Panel was not able to identify a patient population who should receive this treatment preferentially based on available data. The Expert Panel did agree that HD-IL-2 should be administered in experienced high-volume centers, and that enrollment in clinical trials was preferred. ***Recommendation added from the 2023 update:*** • It is strongly advised against administering IpiNivoCabo treatment to patients with metastatic clear cell renal cell carcinoma (ccRCC). Individuals expressing interest in triplet therapy are encouraged to participate in a clinical trial (Evidence quality: High; Strength of recommendation: Strong). **Optimal second- or later-line systemic treatment for metastatic clear cell renal cell carcinoma** • Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone (Evidence quality: High; Strength of recommendation: Strong). • Patients progressing on combination immunotherapy (e.g., nivolumab and ipilimumab) should be offered a VEGFR TKI (Evidence quality: Moderate; Strength of recommendation: Strong). • Patients who progress after initial therapy combining VEGFR TKI with an ICI may be offered an alternate VEGFR TKI as a single agent (Evidence quality: High; Strength of recommendation: Strong). • For patients on immunotherapy who experience limited disease progression (e.g., one site of progression), local therapy (radiation, thermal ablation, and excision) may be offered, and immunotherapy may be continued (Evidence quality: Moderate; Strength of recommendation: Weak).

	Optimal application of metastasis-directed therapy for metastatic clear cell renal cell carcinoma • For patients with low-volume metastatic renal cell carcinoma, definitive metastasis-directed therapies may be offered and include surgical resection (metastasectomy), ablative measures, or radiotherapy (Evidence quality: Moderate; Strength of recommendation: Strong). • For patients undergoing complete metastasectomy, subsequent TKIs are not routinely recommended (Evidence quality: Moderate; Strength of recommendation: Strong). **Considerations for treatment of special subsets of metastatic clear cell renal cell carcinoma (e.g., bone metastases, brain metastases, and sarcomatoid carcinomas)** • Patients with symptomatic bone metastases from metastatic ccRCC should receive bone-directed radiation (Evidence quality: Moderate; Strength of recommendation: Strong). • Patients with bone metastases from metastatic ccRCC should be offered a bone resorption inhibitor (either bisphosphonate or receptor activator of nuclear factor kappa-B ligand inhibitor) when clinical concern for fracture or skeletal-related events is present (Evidence quality: Moderate; Strength of recommendation: Strong). • No recommendation regarding optimal systemic treatment for metastatic ccRCC patients with bone metastasis can be made; however, it is our expert opinion that cabozantinib-containing regimens may be preferred (Evidence quality: Low; Strength of recommendation: Moderate). • Patients with brain metastases from metastatic ccRCC should receive brain-directed local therapy with radiation therapy and/or surgery (Evidence quality: High; Strength of recommendation: Strong). • No recommendation regarding optimal systemic therapy for patients with metastatic ccRCC and brain metastases can be made (Evidence quality: NA; Strength of recommendation: Strong). • Patients with metastatic ccRCC with sarcomatoid features should receive ICI-based

<table>
<tr><td></td><td>combination first-line treatment (ipilimumab plus nivolumab, or alternatively, an ICI plus a TKI; Evidence quality: High; Strength of recommendation: Strong).</td></tr>
<tr><td>Addition of a new section:
European Association of Urology (EAU) Guidelines on Renal Cell Carcinoma (2023) [18]</td><td>Summary of recommendations issued by the EAU for the management of RCC
<table>
<tr><th>Recommendations</th><th>Strength</th></tr>
<tr><td colspan="2">Treatment of localized RCC</td></tr>
<tr><td>Provide surgical intervention for the purpose of achieving a cure in cases of localized renal cell cancer.</td><td>Strong</td></tr>
<tr><td>Recommend partial nephrectomy (PN) for individuals diagnosed with T1 tumors.</td><td>Strong</td></tr>
<tr><td>Consider PN for patients with T2 tumors who have a solitary kidney or chronic kidney disease, if technically feasible</td><td>Weak</td></tr>
<tr><td>Avoid performing ipsilateral adrenalectomy in the absence of clinical evidence indicating invasion of the adrenal gland.</td><td>Strong</td></tr>
<tr><td>Refrain from offering an extended lymph node dissection to patients with organ-confined disease.</td><td>Weak</td></tr>
<tr><td>Suggest embolization for individuals unfit for surgery who present with significant hematuria or flank pain.</td><td>Weak</td></tr>
<tr><td colspan="2">Radical and partial nephrectomy techniques</td></tr>
<tr><td>Recommend laparoscopic radical nephrectomy (RN) for individuals with T2 tumors and localized masses that cannot be treated with partial nephrectomy (PN).</td><td>Strong</td></tr>
<tr><td>Strongly advise against performing minimally-invasive RN in patients with T1 tumors when PN is feasible, regardless of the approach, including open surgery.</td><td>Strong</td></tr>
</table></td></tr>
</table>

	Avoid opting for minimally-invasive surgery if this approach may potentially compromise oncological, functional, and peri-operative outcomes.	Strong
	Consider intensifying follow-up in patients with a positive surgical margin, particularly in those who have been upstaged to pT3a.	Weak
	Therapeutic approaches as alternative to surgery	
	Consider providing active surveillance (AS) or thermal ablation (TA) as options for frail and/or comorbid patients with small renal masses.	Weak
	Prior to thermal ablation (TA), strongly recommend performing a percutaneous renal mass biopsy, and it should be conducted separately, not concomitantly with TA.	Strong
	When offering TA or AS, engage in discussions with patients regarding the potential harms and benefits concerning oncological outcomes and complications.	Strong
	Avoid routinely recommending TA for tumors larger than 3 cm and cryoablation for tumors exceeding 4 cm.	Weak
	Treatment of locally advanced RCC	
	As part of nephrectomy, extract clinically enlarged lymph nodes to assess staging, prognosis, and follow-up implications.	Weak
	In cases of non-metastatic disease with venous involvement, strongly advocate for removing both the renal tumor and thrombus.	Strong
	Engage in comprehensive discussions about treatment options for patients with locally-advanced unresectable renal cell carcinoma (RCC), considering biopsy, systemic therapy, deferred resection, or	Strong

	palliative management. This decision-making process should involve a multidisciplinary team to determine the treatment goal.	
	Neoadjuvant and adjuvant therapy	
	Engage in discussions with patients to explore the contradictory results of available adjuvant immune checkpoint inhibitor (ICI) trials, facilitating shared decision-making.	Strong
	Ensure patients are informed about the potential risks of overtreatment and immune-related side effects if adjuvant therapy is being considered.	Strong
	Strongly discourage the use of adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
	Avoid recommending adjuvant sunitinib for patients with surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak

	Consider offering adjuvant pembrolizumab to ccRCC patients, preferably within 12–16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial:
	• Intermediate-high risk:
	  • pT2, grade 4 or sarcomatoid, N0, M0
	  • pT3, any grade, N0, M0
	• High risk:
	  • pT4, any grade, N0, M0
	  • any pT, any grade, N+, M0
	  • M1 no evidence of disease (NED): NED after resection of oligometastatic sites < 1 year from nephrectomy.
		Weak

	Advanced/metastatic RCC: local therapy	
	Strongly advise against performing cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong

	Avoid immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy.	Weak
	Consider initiating systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy.	Weak
	Encourage discussions about delayed CN with patients who experience clinical benefit from systemic therapy.	Weak
	Consider immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
	Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak
	Local therapy of metastases in metastatic RCC	
	Consider providing ablative therapy, including metastasectomy, to patients with metastatic disease and favorable disease factors, ensuring complete resection is achievable, in order to control local symptoms.	Weak
	Suggest stereotactic radiotherapy as an option for clinically relevant bone- or brain metastases to achieve local control and symptom relief.	Weak
	Strongly discourage the use of tyrosine kinase inhibitor treatment for metastatic renal cell carcinoma (mRCC) patients after metastasectomy and in the absence of evidence of disease.	Strong
	Before proceeding with metastasectomy, conduct a confirmatory axial scan of disease status to rule out rapidly progressive metastatic disease that may necessitate systemic treatment.	Weak

	Prior to initiating systemic therapy for oligometastases that cannot be resected, engage in discussions with the patient about the possibility of observing the condition until progression is confirmed.	Weak
	Systemic therapy in advanced/metastatic RCC	
	Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong
	Single-agent targeted therapy in metastatic clear-cell RCC	
	Strongly recommend offering nivolumab or cabozantinib for immune checkpoint inhibitor-naive, vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
	Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is advisable.	Weak
	Consider VEGF-tyrosine kinase inhibitors as second-line therapy for patients refractory to nivolumab plus ipilimumab, axitinib plus pembrolizumab, cabozantinib plus nivolumab, or lenvatinib plus pembrolizumab.	Weak
	Strongly recommend offering cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
	Emphasize the importance of sequencing systemic therapy in treating metastatic renal cell carcinoma (mRCC).	Strong
	Consider immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
	Immunotherapy in cc-mRCC	
	Treatment-naïve patients	

	Consider offering treatment with PD1 combinations in centers with experience to treatment-naïve patients	Weak
	Strongly recommend offering either nivolumab plus ipilimumab, pembrolizumab plus axitinib, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naive patients with IMDC intermediate- or poor-risk disease.	Strong
	Consider offering either pembrolizumab plus axitinib, lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naïve patients with IMDC favorable risk.	Weak
	Consider offering sunitinib or pazopanib to treatment-naive patients with IMDC favorable risk.	Weak
	Strongly recommend offering sunitinib or pazopanib to treatment-naive clear-cell metastatic renal cell carcinoma (cc-mRCC) patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
	Strongly recommend offering cabozantinib to treatment-naive patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
	Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	Weak
	Sequencing systemic therapy	
	Strongly recommend sequencing systemic therapy in treating metastatic renal cell carcinoma (mRCC).	Strong
	Consider offering VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or	Weak

	axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	
	Consider recommending sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy.	Weak
	Strongly recommend offering nivolumab or cabozantinib to those patients who received first-line VEGF-targeted therapy alone.	Strong
	Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
	Strongly discourage re-challenging patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong
	Targeted therapy in RCC with sarcomatoid features	
	Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
	Targeted therapy in non-clear-cell metastatic RCC	
	Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak
	Targeted therapy in papillary metastatic RCC	
	Consider offering cabozantinib to patients with papillary RCC (pRCC) based on a positive randomized controlled trial (RCT).	Weak
	Consider offering pembrolizumab alone, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak
	Locally recurrent RCC after treatment of localized disease	

	Consider providing local treatment for locally recurrent disease when technically feasible, taking into account adverse prognostic features, comorbidities, and life expectancy.	Weak
	Follow-up in RCC	
	Recommend tailoring the follow-up after the treatment of localized RCC according to the risk of recurrence.	Strong
	Consider intensifying follow-up in patients who undergo nephron-sparing surgery (NSS) for tumors larger than 7 cm or in those with a positive surgical margin.	Weak
	Consider reducing the frequency of follow-up when the risk of death from other causes is twice that of the risk of RCC recurrence.	Weak
Addition of a new section: Canadian Kidney Cancer Forum (CKCF) Consensus Statement on Adjuvant Chemotherapy for Renal Cell Carcinoma (2023) [25]	• Urologists should discuss the risk of cancer recurrence with patients who underwent surgery for RCC, utilizing validated prediction tools. • For adjuvant therapy consideration, patients must have completely removed clear-cell RCC disease (localized, N+M0, or M1 NED). • Patients with surgically removed clear-cell RCC, identified as having a heightened risk of recurrence, should be educated about the possible benefits of adjuvant therapy and provided with the option of consulting a medical oncologist. • Before initiating adjuvant therapy, patients should undergo staging that involves cross-sectional imaging of the chest, abdomen, and pelvis. • In the event of administering adjuvant therapy, it should commence within 12–16 weeks following surgery. • In the case of offering adjuvant therapy, pembrolizumab is presently the sole treatment recommended for consideration. • Consideration for adjuvant systemic therapy may apply to patients with pT2 clear-cell RCC grade 4 or with sarcomatoid features, as well as those with pT3 clear-cell RCC disease.	

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Patients with pT4 clear-cell RCC of any grade and those with N1 clear-cell RCC might be considered for adjuvant systemic therapy.
Patients with resected M1 clear-cell RCC and no evidence of disease (NED) could be considered for adjuvant systemic therapy.
If patients undergo adjuvant pembrolizumab, the treatment duration should last one year.
During adjuvant therapy, patients should undergo follow-up imaging every 3–6 months.
After completing adjuvant therapy, ongoing follow-up surveillance should follow guidelines for localized disease.
Patients experiencing disease recurrence six months or more after finishing adjuvant therapy should be offered standard-of-care first-line treatment for metastatic disease.
Patients experiencing disease recurrence during adjuvant therapy or within six months after completion should be managed similarly to patients progressing on first-line immunotherapy for metastatic disease.

</td></tr>
<tr><td>Addition of a new section: National Comprehensive Care Network (NCCN) Wilms Tumor (v1.2023)[30]</td><td>
Children's Oncology Group (COG) staging of Wilms Tumor
<table>
<tr><th colspan="2">COG staging of Wilms Tumor</th></tr>
<tr><td>Stage I</td><td>Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to
removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection.
Note: For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically</td></tr>
<tr><td>Stage II</td><td>The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends
beyond kidney, as is evidenced by any one of the following criteria:
• There is regional extension of the tumor (i.e. penetration of the renal</td></tr>
</table>
</td></tr>
</table>

		capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. Note: Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.
	Stage III	Residual nonhematogenous tumor present following surgery and confined to abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extraabdominal sites is a criterion for Stage IV.) • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurring either before or during surgery. • The tumor was biopsied (whether tru-cut, open or fine needle aspiration) before removal. • Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).

		Note: Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.
	Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).
	Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease

- Treatment for Wilms tumor (WT) varies and depends on several factors, including whether the tumor is unilateral or bilateral, its local stage, the presence of metastases, the patient's age, tumor weight, biologic risk factors, histology, and clinical response to therapy.
- A multidisciplinary evaluation involving surgeons, pediatric oncologists, and radiation oncologists is recommended before deciding on the treatment approach.
- For most children with suspected WT, **surgery** is recommended, even for those initially considered unresectable or with bilateral or metastatic disease. Risk assessment helps determine the need for and type of adjuvant therapy after surgery. Unilateral nephrectomy is often performed upfront for children with resectable unilateral kidney disease.
- While most cases involve resectable unilateral kidney disease, multifocal unilateral (10%) or primary bilateral renal tumors (5%–13%) are less common.
- **Treatment goals** aim to maximize cure while minimizing long-term toxicity. Long-term risks include secondary malignancy from chemotherapy and/or radiation therapy (RT), as well as the development of end-stage renal disease, among other concerns.

	Neoadjuvant chemotherapy • Neoadjuvant chemotherapy is recommended for children with bilateral Wilms tumor (WT), initially unresectable unilateral tumors, or those with predisposing conditions and either localized or metastatic unilateral renal tumors. • Specific chemotherapy regimens are administered for 6 weeks, followed by tumor response assessment. **Surgery** • Surgery for WT aims to remove all disease without tumor rupture, conduct accurate lymph node staging, and complete pathologic evaluation. • Most patients with favorable histology WT undergo unilateral radical ureteronephrectomy, while nephron-sparing surgery (NSS) is reserved for bilateral disease, genetically predisposed individuals, or those at higher risk for renal failure. • NSS is not recommended for unilateral disease without genetic predisposition. • Surgical tissue specimens undergo testing for diagnosis confirmation, molecular markers, and histology, aiding risk stratification for appropriate adjuvant therapy. • The decision on surgery type and timing, along with the need for neoadjuvant chemotherapy, is essential before treatment. • Contraindications to upfront surgery include tumor extension to contiguous structures, solitary kidney, tumor thrombus above hepatic veins, unacceptable anesthesia risk, or significant pulmonary compromise. • The clinical stage is determined before surgery, with confirmation and complete staging occurring after surgery. **Chemotherapy** • Chemotherapy is proven to enhance the survival of most children with Wilms tumor (WT) when combined with surgery, with or without radiotherapy. • Various chemotherapy regimens, such as **EE4A, DD4A, VAD, regimen M**, and **regimen I**, are employed. Although some agents overlap, the schedules differ, and certain regimens

	serve for neoadjuvant or adjuvant purposes. • The initiation of chemotherapy varies between NWTS studies and COG, but the total number of doses remains consistent. • The specific duration and doses depend on the regimen. • For example, in the EE4A regimen, 13 doses of vincristine and 7 doses of dactinomycin are administered over 18 weeks, while in the DD4A regimen, 15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin are given over 24 weeks. • The choice of regimen is influenced by treatment response and the timing of surgery, with certain regimens reserved for neoadjuvant therapy in patients eligible for nephron-sparing surgery. • Regimen M and regimen I have specific doses and schedules, and their initiation depends on factors such as molecular markers, lung metastasis response, or histology. **Chemotherapy Regimens** • EE4A: 13 doses of vincristine and 7 doses of dactinomycin administered over 18 weeks. • DD4A: 15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin (cumulative dose 150 mg/m2) administered over 24 weeks with alternating doses of dactinomycin and doxorubicin. • VAD: 6–12 doses of vincristine, 2–4 doses of dactinomycin, and 2–4 doses of doxorubicin (cumulative dose 70–140 mg/m2) administered over 6–12 weeks used only in the neoadjuvant setting for patients who are candidates for NSS. In this regimen dactinomycin and doxorubicin are given together.7 • Regimen M: 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m2), 4 cycles of 5 daily doses of cyclophosphamide, and 4 cycles of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on molecular markers or response of lung metastases to 6 weeks of DD4A.

	• Regimen I: 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m2), 7 cycles of 3 to 5 daily doses of cyclophosphamide, and 3 cycles of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on histology. **Neoadjuvant chemotherapy** • Neoadjuvant chemotherapy regimens are employed for patients who cannot undergo upfront nephrectomy. • Options include **EE4A, DD4A, or VAD**. • At the 6th week of neoadjuvant chemotherapy, reimaging assesses tumor resectability. Pulmonary lesions gauge chemotherapy response, with removal considered after 6 weeks if feasible. • Complete response at week 6 eliminates the need for surgery, while less than partial response prompts an open biopsy for anaplasia or confirmation. • For patients with partial response at week 6 but unsuitable for surgery, including nephron-sparing surgery (NSS), chemotherapy continues for 12 weeks. However, clinical trial data advise surgery by week 12, as prolonging chemotherapy beyond 12 weeks doesn't further reduce tumor size. **Adjuvant Chemotherapy** • Regimens for adjuvant chemotherapy encompass: **1) EE4A, 2) DD4A, 3) regimen M, and 4) regimen I** • The specific regimens employed depend on the context and risk stratification. • For instance, children with unilateral favorable histology Wilms tumor (FHWT) at standard risk post-upfront nephrectomy are recommended to receive adjuvant chemotherapy with EE4A. • The commencement of adjuvant chemotherapy should occur within 14 days following nephrectomy.

	• As mentioned earlier, risk stratification guides the selection of the most suitable adjuvant chemotherapy regimens for patients. • In cases where radiation therapy (RT) is necessary, the timing of adjuvant chemotherapy administration should be coordinated to prevent concurrent full doses of dactinomycin or doxorubicin with radiation. **Radiation Therapy** • For suspected Wilms tumor (WT), the NCCN Panel advises early consultation with a radiation oncologist to allow sufficient time for potential radiation planning, coordinating with chemotherapy administration as necessary. • Adjuvant RT is recommended for higher-risk patients post-surgery but is not indicated for those with low-stage, lower-risk disease. • Depending on the scenario, recommendations may include adjuvant flank RT or Whole Abdominal Irradiation (WAI) with or without whole lung irradiation. • For instance, adjuvant flank RT is suggested for patients with local stage III FHWT or stage IV with local stage III. • It's crucial to note that biopsy alone does not elevate a tumor to stage III for determining the need for adjuvant RT. To enhance protection, testicular shielding is advised for most boys undergoing adjuvant flank RT. • WAI is recommended for patients with cytology-positive ascites, any preoperative tumor rupture, peritoneal seeding, and diffuse surgical spillage. • Supplementary boost irradiation is suggested for gross residual disease remaining after adjuvant flank RT or WAI. • Adjuvant whole lung irradiation is indicated for patients with lung metastases, with the option of using intensity-modulated RT (IMRT) or anteroposterior/posteroanterior (AP/PA). However, in select patients with FHWT and lung-only metastases responding completely to 6 weeks of chemotherapy, whole lung irradiation may be omitted. • Nevertheless, it remains recommended for patients with 1q gain or LOH at 1p and 16q.

- Studies emphasize the importance of starting RT within the initial 14 days post-surgery to reduce the risk of abdominal recurrence in metastasis-free patients.
- Ideally, the NCCN Panel suggests starting RT by day 10 after surgery but no later than day 14. Patient-specific factors, including age and the need to assess lung metastases response to chemotherapy when administering WAI and whole lung irradiation, should be considered.
- Coordination between RT and chemotherapy is essential to avoid concurrent administration of full doses of dactinomycin or doxorubicin with RT allowing for the administration of these agents at full doses before the initiation of RT.

Treatment options for Wilms Tumor per individual case presentation

Unilateral renal tumor **Resectable**	**Very low risk** Children with FHWT fitting the criteria of the COG very-low-risk group can be observed without adjuvant therapy or receive adjuvant chemotherapy with EE4A. EE4A is recommended for children with very-low-risk clinical features but with unfavorable prognostic molecular markers (11p15 LOH or LOI or combined LOH at 1p and 16q). Observation only after surgery is recommended for children without these unfavorable biomarkers. Postoperative RT is not recommended for stage I disease. **Low risk** Children with FHWT at low risk after surgery can receive adjuvant therapy with regimen EE4A or switch to regimen DD4A. DD4A is recommended for children with low-risk tumors that express combined LOH 1p and 16q. EE4A can be continued for children with tumors that do not have these unfavorable

		biomarkers. Postoperative RT is not recommended for local stage I and II disease. **Standard risk and higher risk** DD4A is recommended for patients with stage III FHWT classified as standard risk after the initial risk assessment. At week 6 of DD4A, the results of molecular testing from diagnostic tissue are used to determine the final risk assessment and to select further therapy. Switching to augmented therapy with regimen M is recommended for patients with combined LOH of 1p and 16q who are at increased risk. Flank RT or WAI is recommended for patients with local stage III. If RT is being considered, the timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT. DD4A is the initial recommended therapy for higher-risk stage IV FHWT patients. At week 6 of DD4A, molecular testing and imaging results are utilized for the final risk assessment and treatment selection. Augmented therapy with regimen M is advised for patients with specific criteria, such as combined LOH of 1p and 16q or slow incomplete response of lung metastases after 6 weeks of chemotherapy. DD4A continues after week 6 for patients with lung-only metastases showing complete response or extrapulmonary metastases. However, regimen M is associated with increased toxicity risks, including second cancers and infertility. While a recent study switched patients with extrapulmonary metastases to regimen M (AREN0533), the results are pending publication, and this regimen is not currently recommended in this context.

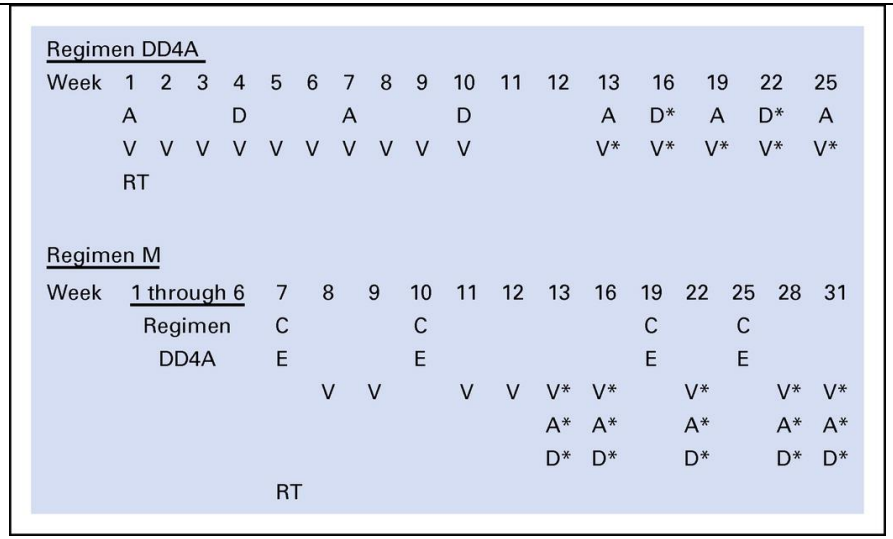
		For patients with local stage III disease having higher risk, postoperative flank RT or WAI is recommended, and whole lung irradiation may be considered based on specific criteria, such as tumors expressing 1q gain or combined LOH at 1p and 16q. Whole lung irradiation is generally recommended for patients with pulmonary metastases, except for those with complete response of pulmonary lesions at 6 weeks and lacking certain risk factors.
	Initially Unresectable Unilateral Renal Tumor with No Predisposing Condition	Neoadjuvant therapy with DD4A is recommended for initially unresectable unilateral renal tumors in children without predisposing conditions. Upfront biopsy, primarily in situations where upfront nephrectomy is contraindicated, is suggested for patients meeting delayed resection criteria, helping establish a WT diagnosis, determine histology, and gather molecular biomarkers for treatment guidance. At week 6 of DD4A, reimaging occurs, and based on tumor response, patients either undergo nephrectomy or continue with DD4A. Chemotherapy continues for 12 weeks if a patient responds but isn't a surgery candidate; however, surgery is recommended by week 12, as prolonged chemotherapy beyond this point typically doesn't further shrink tumors. After confirming FHWT pathology, molecular and imaging results guide the final risk assessment and therapy selection. Patients continue DD4A or switch to regimen M, particularly for those at increased risk, such as those with combined LOH at 1p and 16q or slow-responding lung metastases. While a recent study (AREN0533) switched patients with extrapulmonary metastases to regimen M, results are pending publication, and

		it's not currently recommended in this context. Postoperative flank RT or WAI is recommended for local stage III disease, and whole lung irradiation is advised in certain conditions, including lung metastases resistant to neoadjuvant chemotherapy and specific molecular characteristics. Coordination of RT timing with chemotherapy is crucial to avoid coadministration of full doses of dactinomycin or doxorubicin with RT.
	Localized Unilateral Renal Tumor With a Predisposing Condition	Neoadjuvant therapy with the EE4A regimen is advised for children with a localized unilateral renal tumor and a predisposing condition, discouraging upfront biopsy or resection in this context. If upfront biopsy was performed, the VAD regimen is used for neoadjuvant therapy. At week 6 of EE4A (or VAD), depending on the response, patients may undergo no surgery with complete response, partial nephrectomy if the tumor is now resectable, continue with EE4A (or VAD) for 12 weeks if still unresectable but with partial response, or have complete nephrectomy if there's less than a partial response. If less than a partial response at week 6, a biopsy to confirm FHWT (or WT without anaplasia) is recommended before continuing with EE4A (or VAD). Surgery is performed at 12 weeks, as continuing chemotherapy beyond this period typically doesn't further shrink tumors. The decision for partial or total nephrectomy at week 12 depends on factors like tumor size, location, extension into the kidney collecting system, and other considerations.
	Metastatic Unilateral Renal Tumor With a Predisposing Condition	Neoadjuvant therapy with the VAD regimen is recommended for children with a predisposing condition and a unilateral renal tumor that has metastasized, discouraging upfront biopsy or

			resection. At week 6 of VAD, based on the response, patients may undergo no surgery with complete response, partial nephrectomy if the tumor is now resectable, or continue with VAD for 12 weeks if the tumor is unresectable but with at least a partial response. If less than a partial response at week 6, a biopsy to confirm FHWT (or WT without evidence of anaplasia) is recommended before continuing with VAD. Surgery is performed at 12 weeks, as continuing chemotherapy beyond this period usually doesn't yield continued tumor shrinkage. A partial or total nephrectomy with regional lymph node sampling is recommended at week 12, depending on factors such as tumor size and location. After confirming FHWT, histology (blastemal predominant) is used to guide further therapy. Switching to regimen DD4A is recommended for patients without blastemal predominant histology or those with a complete response at 6 weeks. Augmented therapy with regimen I is recommended for patients with blastemal predominant histology due to their higher risk. Regimen M has not been studied in this population. The timing of radiation therapy (RT) is often 10 to 14 days after surgery, considering the patient's age and other factors. Local stage III, referring to the primary tumor staging regardless of metastases, determines the need for flank RT or WAI. Biopsy alone does not upstage a tumor to stage III. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting, and the omission of whole lung irradiation based on the response of lung metastases at week 6 of neoadjuvant chemotherapy has not been studied in this patient group.

	Bilateral renal tumors	For children with **localized bilateral renal tumors**, neoadjuvant therapy using the VAD regimen is recommended, discouraging upfront biopsy or resection. Surgery is performed at either 6 or 12 weeks after neoadjuvant chemotherapy based on response, considering that continuing beyond 12 weeks usually does not yield additional tumor shrinkage. Preservation of renal function is prioritized, favoring NSS with either bilateral partial nephrectomies or total nephrectomy and contralateral partial nephrectomy. At week 6 of VAD, based on response, patients may undergo no surgery, bilateral partial nephrectomies, or continue with VAD for a total of 12 weeks if tumors are unresectable. If less than a partial response at week 6, renal biopsies in both kidneys are recommended to determine histology before continuing with VAD. After confirming FHWT, staging and histology guide further therapy. Molecular biomarkers are not studied in this setting. Patients switch to EE4A, DD4A, or regimen I based on risk assessment. RT is often administered 10 to 14 days after surgery, considering the patient's age and other factors. Local stage III, regardless of metastases, determines the need for flank RT or WAI. Upfront biopsy does not upstage a tumor to stage III for determining RT. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting, and patients with a complete response at 6 weeks do not require RT. Neoadjuvant therapy using the VAD regimen is recommended for children with metastatic bilateral renal tumors, irrespective of a predisposing condition. Upfront biopsy or resection is discouraged, and the decision for surgery at either 6 or 12 weeks

			is based on the response to chemotherapy, with NSS recommended when feasible. Post-chemotherapy, patients are stratified based on histology (blastemal predominant), and treatment is tailored accordingly. Regimen DD4A or regimen I is chosen, with DD4A for those without blastemal predominant histology or complete response at 6 weeks, and augmented therapy with regimen I for those with blastemal predominant histology. Molecular biomarkers' use in this context hasn't been studied. Radiation therapy, including flank RT or WAI, is considered based on local stage III criteria, and whole lung irradiation may be administered for lung metastases and extrapulmonary sites requiring radiation. Patients with a complete response at 6 weeks post-chemotherapy might not need radiation.
	Treatment regimens used for Wilms Tumor[31]:		



Regimen DD4A

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	16	19	22	25
	A			D			A			D			A	D*	A	D*	A
	V	V	V	V	V	V	V	V	V	V			V*	V*	V*	V*	V*
	RT																

Regimen M

Week	1 through 6	7	8	9	10	11	12	13	16	19	22	25	28	31
	Regimen	C			C					C		C		
	DD4A	E			E					E		E		
			V	V		V	V	V*	V*		V*		V*	V*
								A*	A*		A*		A*	A*
								D*	D*		D*		D*	D*
		RT												

V: vincristine: 0.025 mg/kg/dose intravenously (IV) × 1 for infants < 1 year; 0.05 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 1.5 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg).
V(*): vincristine: 0.034 mg/kg/dose IV × 1 for infants < 1 year; 0.067 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 2 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg).
A: dactinomycin 0.023 mg/kg/dose IV × 1 for infants < 1 year; 0.045 mg/kg/dose IV × 1 for children ≥ 1 year (maximum dose: 2.3 mg).
D: doxorubicin 1.5 mg/kg/dose IV × 1 for infants < 1 year; 45 mg/m^2/dose IV × 1 for children ≥ 1 year.
D(*): doxorubicin 1 mg/kg/dose IV × 1 for infants < 1 year; 30 mg/m^2/dose IV × 1 for children ≥ 1 year.
C: cyclophosphamide 14.7 mg/kg/dose IV × 5 days for infants < 1 year; 440 mg/m^2/dose IV × 5 days for children ≥ 1 year.
E: etoposide 3.3 mg/kg/dose IV × 5 days for infants < 1 year; 100 mg/m^2/dose IV × 5 days for children ≥ 1 year.

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Filters	Search Details	Results
(((Carcinoma, Renal Cell[MeSH Terms])) OR (Carcinomas, Renal Cell[Title/Abstract])) OR (Renal Cell Carcinomas[Title/Abstract])) OR (Nephroid Carcinoma[Title/Abstract])) OR (Carcinoma, Nephroid[Title/Abstract])) OR (Adenocarcinoma Of Kidney[Title/Abstract])) OR (Adenocarcinoma Of Kidneys[Title/Abstract])) OR (Kidney, Adenocarcinoma Of[Title/Abstract])) OR (Renal Cell Carcinoma[Title/Abstract])) OR (Renal Cell Cancer[Title/Abstract])) OR (Cancer, Renal Cell[Title/Abstract])) OR (Renal Cell Cancers[Title/Abstract])) OR (Adenocarcinoma, Renal[Title/Abstract])) OR (Renal Adenocarcinoma[Title/Abstract])) OR (Renal Adenocarcinomas[Title/Abstract])) OR (Renal Carcinoma[Title/Abstract]))	Guideline, in the last 5 years	("carcinoma, renal cell"[MeSH Terms] OR "carcinomas renal cell"[Title/Abstract] OR "renal cell carcinomas"[Title/Abstract] OR ("Nephroid"[All Fields] AND "Carcinoma"[Title/Abstract]) OR (("Carcinoma"[MeSH Terms] OR "Carcinoma"[All Fields] OR "Carcinomas"[All Fields] OR "carcinoma s"[All Fields]) AND "Nephroid"[Title/Abstract]) OR "adenocarcinoma of kidney"[Title/Abstract] OR "adenocarcinoma of kidneys"[Title/Abstract] OR "kidney adenocarcinoma of"[Title/Abstract] OR "renal cell carcinoma"[Title/Abstract] OR "renal cell cancer"[Title/Abstract] OR "cancer renal cell"[Title/Abstract] OR "renal cell cancers"[Title/Abstract] OR "adenocarcinoma renal"[Title/Abstract] OR "renal adenocarcinoma"[Title/Abstract] OR "renal adenocarcinomas"[Title/Abstract] OR "renal carcinoma"[Title/Abstract] OR "carcinoma renal"[Title/Abstract] OR "renal carcinomas"[Title/Abstract] OR "adenocarcinoma renal cell"[Title/Abstract] OR "adenocarcinomas renal cell"[Title/Abstract] OR "renal cell	30 results

OR (Carcinoma, Renal[Title/Abstract])) OR (Renal Carcinomas[Title/Abstract])) OR (Adenocarcinoma, Renal Cell[Title/Abstract])) OR (Adenocarcinomas, Renal Cell[Title/Abstract])) OR (Renal Cell Adenocarcinoma[Title/Abst ract])) OR (Renal Cell Adenocarcinomas[Title/Ab stract])) OR (Chromophobe Renal Cell Carcinoma[Title/Abstract])) OR (Sarcomatoid Renal Cell Carcinoma[Title/Abstract])) OR (Papillary Renal Cell Carcinoma[Title/Abstract])) OR (Renal Cell Carcinoma, Papillary[Title/Abstract])) OR (Chromophil Renal Cell Carcinoma[Title/Abstract])) OR (Grawitz Tumor[Title/Abstract])) OR (Tumor, Grawitz[Title/Abstract])) OR (Clear Cell Renal Carcinoma[Title/Abstract])) OR (Carcinoma, Hypernephroid[Title/Abstra ct])) OR (Hypernephroid Carcinoma[Title/Abstract])) OR (Hypernephroid Carcinomas[Title/Abstract])) OR (Hypernephroma[Title/Abs tract])) OR (Hypernephromas[Title/Ab		adenocarcinoma"[Title/Abstra ct] OR "renal cell adenocarcinomas"[Title/Abstr act] OR "chromophobe renal cell carcinoma"[Title/Abstract] OR "sarcomatoid renal cell carcinoma"[Title/Abstract] OR "papillary renal cell carcinoma"[Title/Abstract] OR "renal cell carcinoma papillary"[Title/Abstract] OR "chromophil renal cell carcinoma"[Title/Abstract] OR "grawitz tumor"[Title/Abstract] OR "tumor grawitz"[Title/Abstract] OR "clear cell renal carcinoma"[Title/Abstract] OR "carcinoma hypernephroid"[Title/Abstract] OR "hypernephroid carcinoma"[Title/Abstract] OR "hypernephroid carcinomas"[Title/Abstract] OR "Hypernephroma"[Title/Abstra ct] OR "Hypernephromas"[Title/Abstr act] OR (("carcinoma, renal cell"[MeSH Terms] OR ("Carcinoma"[All Fields] AND "Renal"[All Fields] AND "Cell"[All Fields]) OR "renal cell carcinoma"[All Fields] OR ("Collecting"[All Fields] AND "Duct"[All Fields] AND "Carcinoma"[All Fields]) OR "collecting duct carcinoma"[All Fields]) AND "Kidney"[Title/Abstract]) OR (("carcinoma, renal cell"[MeSH Terms] OR ("Carcinoma"[All Fields] AND "Renal"[All Fields] AND "Cell"[All Fields]) OR "renal cell carcinoma"[All Fields] OR ("Carcinoma"[All Fields] AND "Collecting"[All	

stract])) OR (Collecting Duct Carcinoma (Kidney[Title/Abstract]))) OR (Carcinoma, Collecting Duct (Kidney[Title/Abstract]))) OR (Carcinomas, Collecting Duct (Kidney[Title/Abstract]))) OR (Collecting Duct Carcinomas (Kidney[Title/Abstract]))) OR (Collecting Duct Carcinoma of the Kidney[Title/Abstract])) OR (Renal Collecting Duct Carcinoma[Title/Abstract])) OR (Collecting Duct Carcinoma[Title/Abstract])) OR (Carcinoma, Collecting Duct[Title/Abstract])) OR (Carcinomas, Collecting Duct[Title/Abstract])) OR (Collecting Duct Carcinomas[Title/Abstract])		Fields] AND "Duct"[All Fields]) OR "carcinoma collecting duct"[All Fields]) AND "Kidney"[Title/Abstract]) OR (("carcinoma, renal cell"[MeSH Terms] OR ("Carcinoma"[All Fields] AND "Renal"[All Fields] AND "Cell"[All Fields]) OR "renal cell carcinoma"[All Fields] OR ("Carcinomas"[All Fields] AND "Collecting"[All Fields] AND "Duct"[All Fields]) OR "carcinomas collecting duct"[All Fields]) AND "Kidney"[Title/Abstract]) OR (("carcinoma, renal cell"[MeSH Terms] OR ("Carcinoma"[All Fields] AND "Renal"[All Fields] AND "Cell"[All Fields]) OR "renal cell carcinoma"[All Fields] OR ("Collecting"[All Fields] AND "Duct"[All Fields] AND "Carcinomas"[All Fields]) OR "collecting duct carcinomas"[All Fields]) AND "Kidney"[Title/Abstract]) OR "collecting duct carcinoma of the kidney"[Title/Abstract] OR "renal collecting duct carcinoma"[Title/Abstract] OR "collecting duct carcinoma"[Title/Abstract] OR "carcinoma collecting duct"[Title/Abstract] OR "carcinomas collecting duct"[Title/Abstract] OR "collecting duct carcinomas"[Title/Abstract]) AND (y_5[Filter])	

Appendix D. Treatment Algorithms

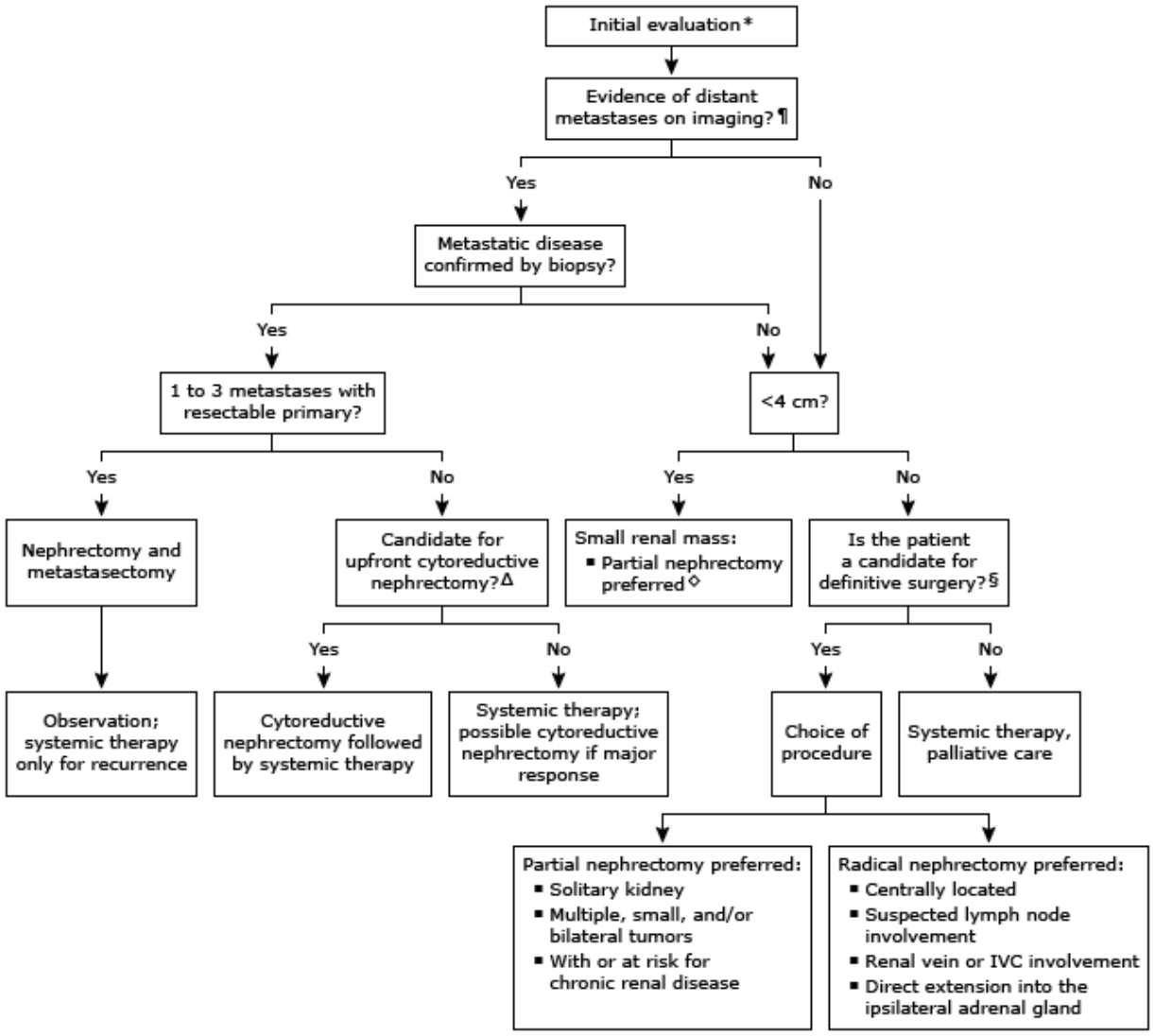


Figure 1. Treatment algorithm of localized renal cell carcinoma

IVC: inferior vena cava; CT: computed tomography; MRI: magnetic resonance imaging.
* Preliminary diagnosis is based upon characteristic findings on imaging studies (CT/MRI); tissue diagnosis is generally obtained at time of definitive surgery.
¶ Chest imaging, additional studies as clinically indicated to look for evidence of metastases.
Δ Selection of patients should be done with considerable care so that appropriate patients can proceed with systemic therapy; important factors include good performance status, ability to perform adequate debulking, and favorable- or low-

intermediate-risk diseases.
◊ Partial nephrectomy is the preferred approach to confirm the diagnosis and treat a renal mass <4 cm. However, thermal ablation (cryotherapy, radiofrequency ablation) or active surveillance may be appropriate alternatives for patients who are not surgical candidates. The choice between these approaches is guided by local expertise and patient preference.
§ Based upon factors including patient preference, age, and comorbidities.

Metastatic/Advanced:

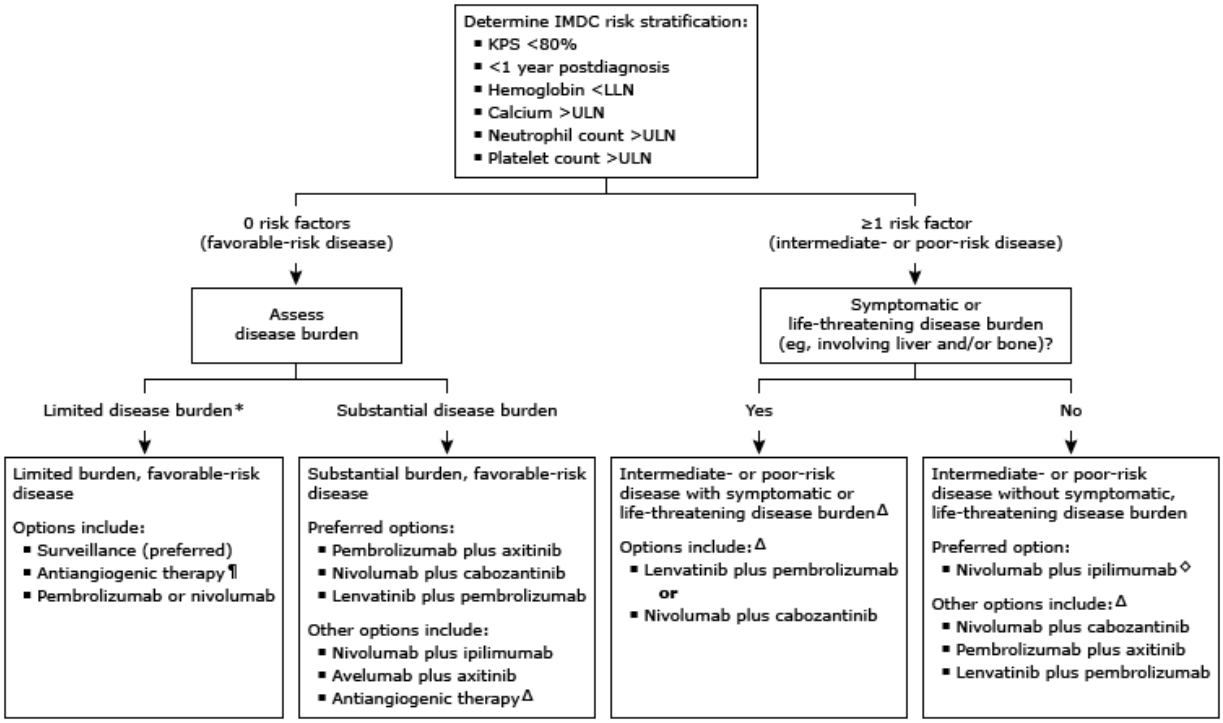


Figure 2. Treatment Algorithm of metastatic/advanced renal cell carcinoma

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; VEGFR: vascular endothelial growth factor receptor.

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

¶ For patients with limited burden, favorable-risk disease who desire a more aggressive management approach, options for antiangiogenic therapy include sunitinib or pazopanib.

Δ For patients who are ineligible for or decline initial treatment with immunotherapy combinations, we offer antiangiogenic therapy that incorporates a VEGFR inhibitor. For patients with substantial burden, favorable risk disease, options include lenvatinib plus everolimus, sunitinib, and pazopanib. For those with intermediate or poor-risk disease, options include lenvatinib plus everolimus or cabozantinib.

◊ Nivolumab plus ipilimumab offers the opportunity for curative intent therapy through durable responses, preserving overall survival benefit, and improving treatment-free survival. By indirect comparison of randomized trials, nivolumab plus ipilimumab confers these treatment benefits to a greater degree than combination immunotherapy plus antiangiogenic therapy, despite having a relatively lower objective response rate. For patients who are not anticipated to tolerate the toxicities of nivolumab plus ipilimumab, immunotherapy plus antiangiogenic therapy is an appropriate alternative.

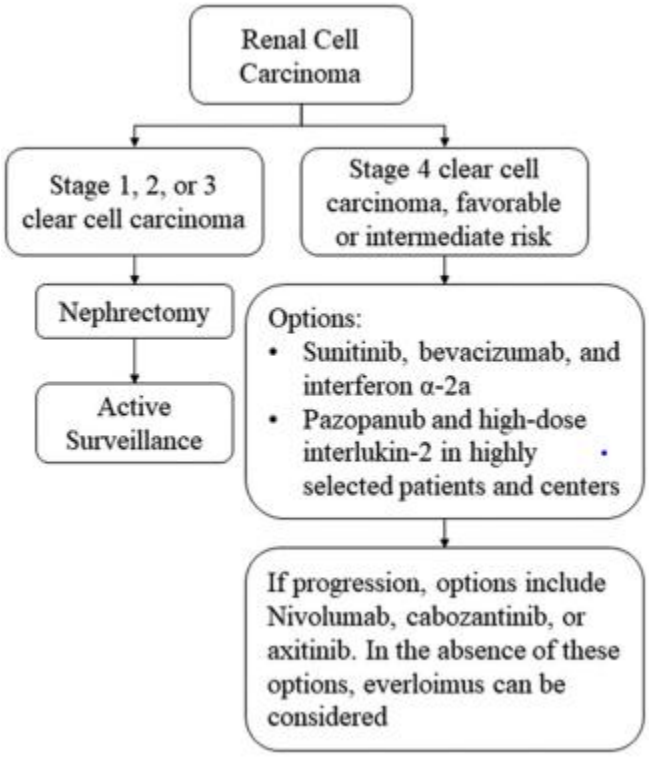


Figure 3. Renal Cell Carcinoma management diagram as per Saudi Guidelines

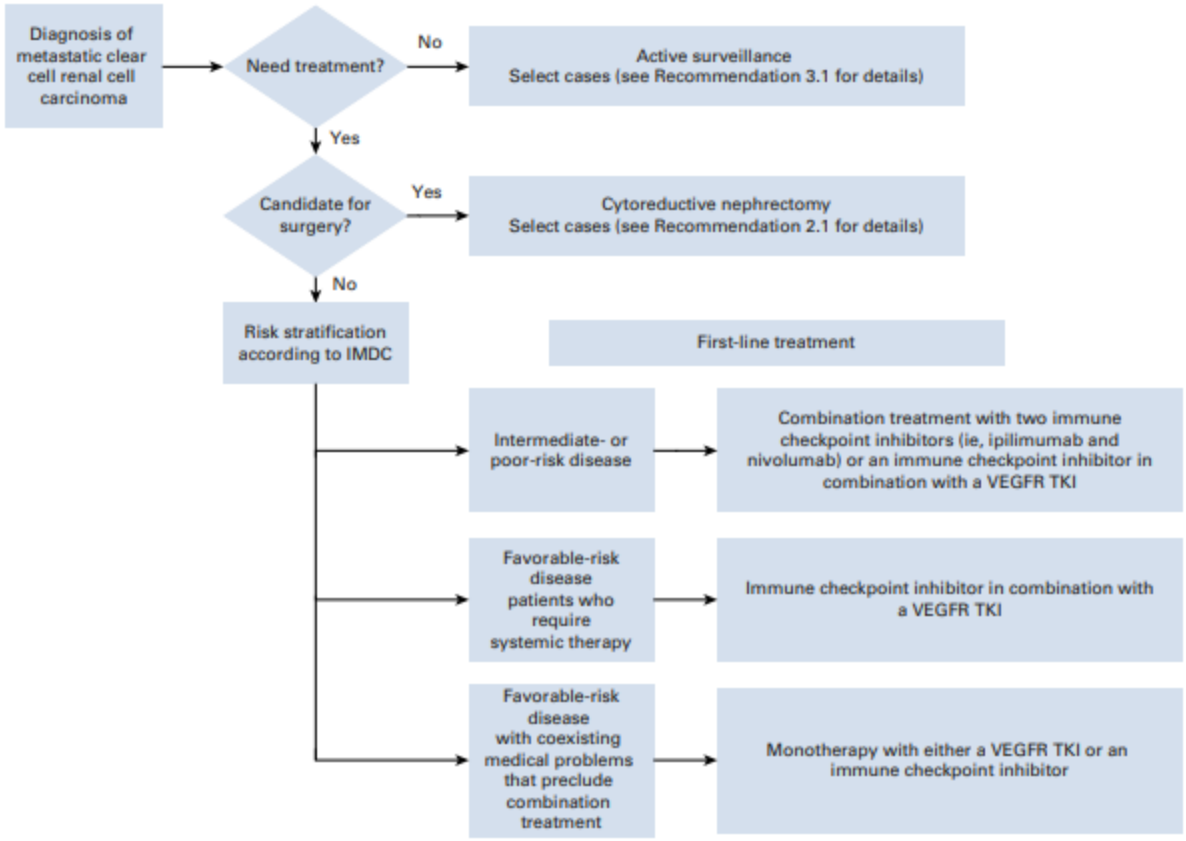


Figure 4. First-line treatment options for renal cell carcinoma

IMDC: International Metastatic RCC Database Consortium

VEGFR TKI: vascular endothelial growth factor receptor

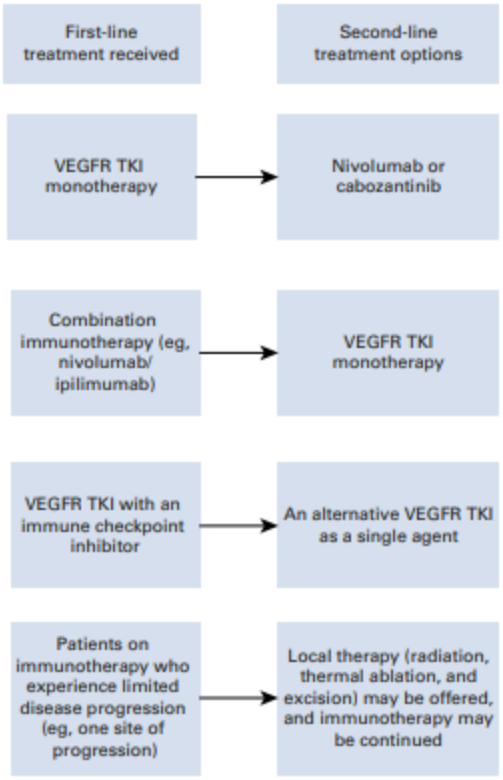


Figure 5. Second-line or greater treatment options for renal cell carcinoma

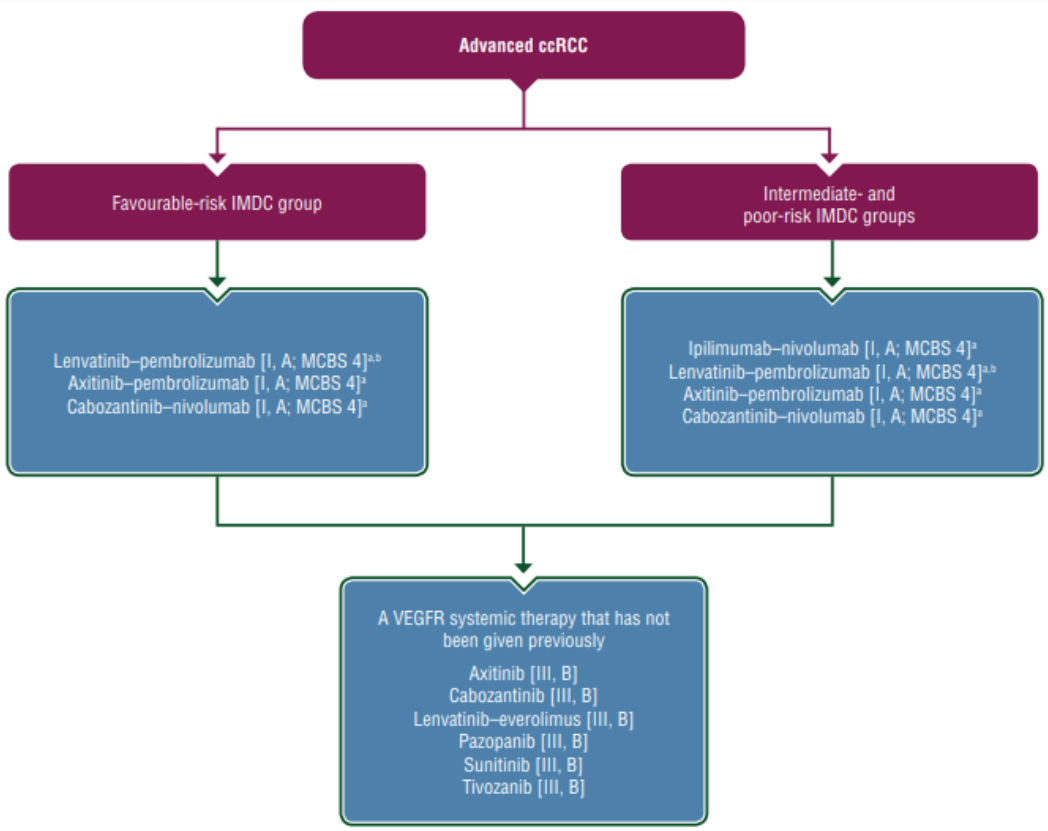


Figure 6. Treatment algorithm for advanced ccRCC

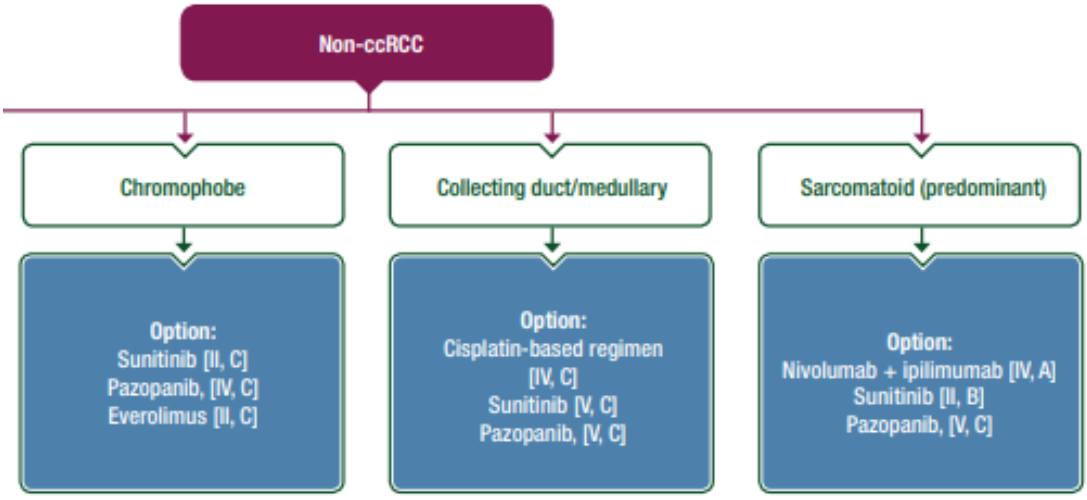


Figure 7. Treatment algorithm for non-ccRCC