

Treatment for advanced renal cell carcinoma (RCC)



What is advanced renal cell carcinoma?

Advanced renal cell carcinoma (RCC) is cancer that has spread from the kidney to other parts of the body. Often people with RCC have no symptoms until the tumour has reached the advanced stages of the disease. Around 25-30% of patients don't find out they have RCC until the cancer has already spread outside the kidney capsule and they have symptoms, such as blood in the urine, weight loss, shortness of breath, bone pain or bone fracture.

Surgeons and oncologists often refer to advanced kidney cancer as either locally advanced or metastatic. These are described in more detail below:

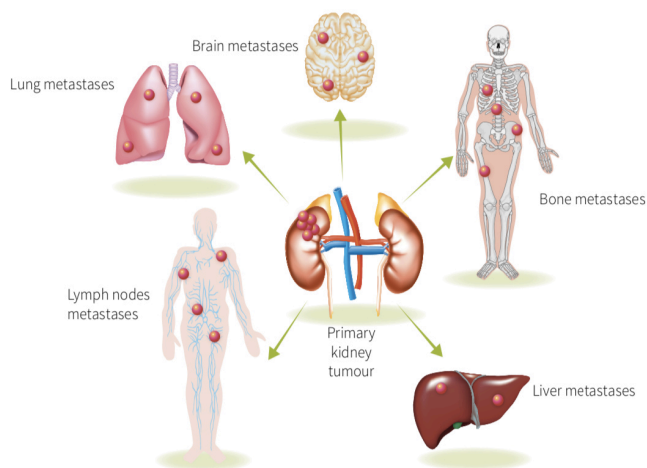
Locally advanced RCC is where the original primary tumour has grown into nearby tissue, such as the adrenal gland, lymph nodes or blood vessels. People with locally advanced disease are considered to have stage III RCC (see *Essential guide: Staging and grading of kidney cancer for a definition of the various stages of RCC*).

Locally advanced RCC is defined as growing into the following areas of the body:

- Through the kidney capsule and into the fat around the kidney
- The major veins close to the kidney (the renal vein or the vena cava)
- Adrenal gland
- Local lymph nodes (not in all cases)

People with locally advanced RCC usually have a large primary tumour of more than 10 cm in diameter, or they may have 3 or 4 smaller tumours on one kidney. If a biopsy of the tumour tissue is taken after surgery (see *Essential guide: Diagnosis and tests for kidney cancer for information about biopsy*) cancer cells are often found at the edge of the tissue sample that was removed during surgery (called a positive margin).

Metastatic RCC is cancer that has spread from the original primary tumour in the kidney to other distant organs and tissues in the body. When the cancer spreads to other parts of the body it



forms small tumours, called metastases, within the organs and tissues where it has spread to. The cells of these metastases look like kidney cells under the microscope, regardless of which organ or tissue they spread to.

People with metastatic RCC are considered to have stage IV RCC (see *Essential guide: Staging and grading of kidney cancer for a definition of the various stages of RCC*).

RCC can spread into the following areas of the body:

- Local and distant lymph nodes
- Nearby organs such as the adrenal glands, liver, spleen, colon or pancreas
- Lungs
- Bone
- Brain
- Liver

What is performance status?

Your oncologist may use a scoring system to help predict the outcome or prognosis of your cancer and to determine your general health or performance status. This may help your oncologist plan the best treatment for you.

Your general health might be assessed using a performance status score. The Eastern Cooperative Oncology Group (ECOG) score is a scale for the measurement of performance. It is used to assess how your cancer is progressing, how the disease affects your day-to-day life, and to help determine appropriate treatment and outcomes. Your oncologist will grade you, as follows:

1. Fully active, able to carry on all pre-disease performance without restriction
2. Restricted in physically strenuous activity but able to walk and carry out work of a light or sedentary nature, e.g., light housework, office work
3. Able to walk and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
4. Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
5. Completely disabled; cannot carry out any selfcare; totally confined to bed or chair.

What is a prognostic score?

Occasionally, your oncologist will assess the outcome or prognosis of your cancer. Various scoring systems are used, one of which is the Leibovich score. This is a scoring algorithm that can be used to predict cancer-specific survival for patients with metastatic kidney cancer. The scoring system is based on the stage of disease,



spread to the lymph nodes, tumour size, grade and the amount of dead tumour tissue (tumour necrosis). A low score (0-2) is a good prognosis, a score of 2-6 is an intermediate prognosis, and a high score (6-11) is a poor prognosis.

What is adjuvant therapy?

Adjuvant therapy can be given to patients after surgery for locally advanced RCC to lessen the chance of your cancer coming back. Even if your surgery was successful at removing all visible cancer, microscopic cancer cells can sometimes remain. They cannot be seen by the naked eye and are undetectable with current methods.

Adjuvant therapy is usually only offered as part of a clinical trial. Some targeted therapies (see below) have been tested as adjuvant therapies, but without success. Adjuvant trials with immunotherapies are ongoing.

Surgery for advanced RCC

If your kidney cancer has spread to other parts of the body, surgery may still be useful to relieve symptoms such as pain, bleeding or to help control the chemical balance in the blood. This sort of surgery does not usually offer a cure so it is important to think carefully about the risks and benefits it may bring. Sometimes, if there is spread to just the lungs or liver, the metastatic tumours can be removed by surgery. This is called a metastasectomy. Removing the metastases can also improve survival time. See *Essential guide: Surgery for kidney cancer* for information about the types of surgery available for kidney cancer.

What are the treatments for advanced RCC?

A number of biological and targeted therapies are used for the treatment of advanced RCC, including immunotherapies, targeted therapies and monoclonal antibodies. These are sometimes called systemic therapies because they travel through the blood stream (or blood system) to reach the cancer cells.

Biological therapies are medications made from natural substances found in the body. These are used to kill cancer cells or stop them from growing. Biological therapies can shrink or control the cancer and help people live longer. You will be given a biological therapy for kidney cancer that has already spread or for locally advanced kidney cancer that is at high risk of coming back after surgery.

Some people with advanced kidney cancer respond very well to biological therapies, and the treatment can control their cancer for a number of months or even years. To improve survival, people are given these medications one after the other (in sequence) when each medication stops working. Some of these medications are given together (in combination) with other medications, again to extend survival. Research into the

best combination or sequence of medications for the treatment of kidney cancer is ongoing.

Taking medication for the treatment of RCC is an option for most people with metastatic RCC. Some medications might not be suitable for people with multiple serious diseases or conditions (co-morbidities). You will need to discuss your suitability for RCC medication with your oncologist to make an informed decision about which option to choose.

Targeted therapies

One of the most promising advances in the treatment of kidney cancer has been the development of targeted therapies, such as vascular endothelial growth factor (VEGF) inhibitors (sometimes called tyrosine kinase inhibitors, TKIs) and mammalian target of rapamycin (mTOR) inhibitors. These medications are now standard treatment for advanced kidney cancer.

Vascular endothelial growth factor (VEGF) inhibitors block the effects of a protein called tyrosine kinase, which is involved in new blood vessel growth that is essential for cancer cells to divide and grow. These treatments starve the tumour by stopping the development of a new blood supply (angiogenesis). VEGF inhibitors also interfere with the growth of cancer cells by blocking the signals within the cancer cells that tell them to grow and divide, causing the cancer cells to die.

Specific **monoclonal antibodies (MAb)** can also be used as VEGF inhibitors. In the UK, VEGF inhibitors are often used as the first treatment after surgery, i.e., first-line treatment. However, they can also be used as second- or third-line treatments after earlier treatments have stopped working or aren't tolerated.

Mammalian target of rapamycin (mTOR) inhibitors act in a similar way to VEGF inhibitors by interfering with the signalling pathway that controls tumour cell growth and the development of a new blood supply to the tumour.

In the UK, mTOR inhibitors are used as second- or third-line

treatments after earlier treatments have stopped working or aren't tolerated. The mTOR inhibitor, temsirolimus, can also be used to treat patients with a poor outlook (prognosis).

The following table summarises the targeted therapies available in the UK for the treatment of advanced kidney cancer, along with the common side effects for each treatment:

Immunotherapy

Immunotherapy stimulates the immune system to attack cancer cells. It uses man-made copies of substances that are found naturally in the body. These include substances called cytokines and others called immune checkpoint inhibitors. Cytokines are now rarely used for the treatment of kidney cancer, and have been superseded by more effective treatments, such as targeted therapies and immune checkpoint inhibitors.

	Targeted therapy			
Type of medication	Vascular endothelial growth factor (VEGF) inhibitors: Tyrosine kinase inhibitors (TKI)	Vascular endothelial growth factor (VEGF) inhibitors: Monoclonal antibodies (MAb)	Mammalian target of rapamycin (mTOR) inhibitors	
Examples of this medication	axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, tivozanib	Bevacizumab (taken with interferon-alpha)	everolimus	temsirolimus
How is it given?	Tablets on a daily basis, sometimes with breaks in treatment for 1-2 weeks	Bevacizumab is injected into a vein every 2 weeks. Interferon needs to be injected under the skin 3 times a week	Daily tablet	Injected into a vein once a week
How does it work?	Prevents growth of cancer cells and blood vessels to the tumour	Prevents growth of cancer cells and blood vessels to the tumour	Prevents growth of cancer cells	
What are the more common side effects?	Fatigue, diarrhoea, nausea and vomiting, stomach pain, weight loss, high blood pressure, tenderness, blisters and extreme sensitivity in the hands and feet (hand - foot syndrome), skin rash, mouth sores, taste changes, pain and swelling in arms or legs (oedema), chest pain and breathing problems	Headache, back pain, diarrhoea, loss of appetite, cold symptoms (stuffy nose, sneezing, sore throat, dry or watery eyes), dry or flaky skin, hair loss, changes in your sense of taste, jaw pain, swelling, numbness, loose teeth and gum infection	Fatigue, diarrhoea, decreased appetite, nausea, diabetes, mouth sores, skin rash, swelling in arms or legs (oedema), cough, breathing problems and possible allergic reaction (temsirolimus)	

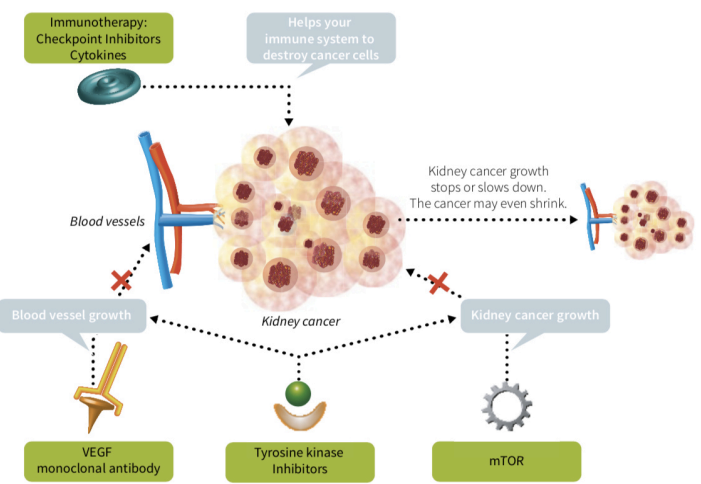
Cytokine therapy

Interferon-alpha works by helping to stop the cancer cells from growing, and by boosting the immune system to attack the cancer. Interferon-alpha is usually given three times a week by an injection under the skin using a very fine needle.

Interleukin 2 (IL 2) or **aldesleukin** stimulates a type of white blood cell, called a T-lymphocyte, to attack the cancer. T-lymphocytes are part of the immune system. A high dose of interleukin 2 is usually given in hospital through a drip into a vein in the arm. Because the side effects to high dose interleukin 2 (HD IL 2) can be serious, it is only given to people who are otherwise



healthy and well enough to withstand the severe side effects. It is also only available at the Christie Hospital in Manchester. A small minority of patients (about 5%) have a long-term durable response to high doses of interleukin 2. Interleukin 2, therefore, still has a place in the treatment of a small percentage of patients where it offers the hope of durable remission.



Immune checkpoint inhibitors

Immune checkpoint inhibitors are a type of immunotherapy. They work by helping the immune system attack cancer cells. Cancer can sometimes push a stop button on the immune cells, so the immune system won't attack them. These medicines block different proteins on the surface of cancer cells called checkpoint proteins. This stops cancers from pushing the stop button for the immune system, allowing the immune system to attack the cancer cells. Immune checkpoint inhibitors are also sometimes named after checkpoint proteins – for example, CTLA-4 inhibitors, PD-1 inhibitors and PD-L1 inhibitors.

Immune checkpoint inhibitors are given alone or in combination with other checkpoint inhibitors or targeted therapies. Most are used as the first treatment after surgery; however, they can be given as second- or third-line treatments. Usually, immunotherapy treatment is given in hospital.

What are the side effects of RCC medications?

These are powerful medicines, and each medication for advanced RCC has different possible side effects. Many of these side effects do not affect everyone. You may only have one or two side effects, or you may not have any at all. If they do occur, they may be mild or temporary, but others may be serious and long lasting and need medical attention. A side effect may get worse through your course of treatment, or more side effects may develop as the course goes on. Many of the side effects can be controlled with medication or well managed, providing they are notified to your hospital team promptly.

Your clinical nurse specialist (specialist nurse) or oncologist should give you a contact number for you to ring if you are worried about

	Immunotherapy		
Medication type	Cytokines		Immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4 inhibitors)
Examples of this medication	High dose Interleukin 2 (HD IL 2)	interferon-alpha (given alone or in combination with bevacizumab)	Nivolumab, ipilimumab, pembrolizumab, avelumab
How is it given?	Injected into a vein through a peripherally inserted central catheter (PICC) every 8 hours for up to 4 days followed by 10 days rest at home and the treatment is repeated over several weeks	Injected under the skin or into a vein 3 times a week	Injected into a vein every 2 or 4 weeks
How does it work?	Helps your immune system attack the cancer cells	Helps your immune system attack the cancer cells	Helps your immune system attack the cancer cells
What are the more common side effects?	Side effects can be severe and dangerous. IL-2 is only given in some countries and select hospitals. Side effects include, rigors, extreme fatigue, fever, low blood pressure, extreme water retention, breathing and heart problems and intestinal bleeding	Flu-like symptoms, fatigue and nausea. Side effects are not as severe as IL-2	Fatigue, rash and other skin reactions, diarrhoea, abdominal pain, loss of appetite, anaemia, fever, stiff or painful joints, numbness, weakness, shortness of breath, chest pain, and sore and red eyes, immune-related adverse effects

side effects or have any questions. You need to tell your healthcare team about your side effects immediately so they can help you manage them. Early reporting can help to minimise the impact of side effects on your health and quality of life and may help you stay on medication longer. You also need to tell your oncologist about any other medicines or complementary treatments you are taking, including vitamins, herbal supplements, special diets and over-the-counter remedies,

	Combination therapies		
Type of medication	Immunotherapy-immunotherapy	Immunotherapy-TKI	
Examples of this medication	ipilimumab plus nivolumab	pembrolizumab plus axitinib	avelumab plus axitinib
How is it given?	ipilimumab and nivolumab are injected into a vein every 3 weeks for a total of 4 doses. After this nivolumab is injected every 2 weeks	pembrolizumab is injected into a vein every 3 weeks and axitinib is taken as a tablet on a daily basis	avelumab is injected into a vein every 2 weeks and axitinib is taken as a tablet on a daily basis
How does it work?	Helps your immune system attack the cancer cells	Helps your immune system attack the cancer cells and prevents growth of cancer cells and blood vessels to the tumour	Helps your immune system attack the cancer cells and prevents growth of cancer cells and blood vessels to the tumour
What are the more common side effects?	Fatigue, rash and itching of the skin, diarrhoea, pain in the muscles, bones and joints, nausea, cough, high temperature, vomiting, breathing difficulties, decreased appetite and inflammation such as colitis, pneumonitis, nephritis	Diarrhoea, fatigue, weakness/lack of energy, high blood pressure, low activity of the thyroid gland, decreased appetite, liver damage, hand-foot syndrome, nausea, inflammation of the mouth and lips, difficulty speaking, rash, cough and constipation	Diarrhoea, fatigue, high blood pressure, pain in the muscles and bones, nausea, inflammation and ulceration of the membranes of the gut, hand-foot syndrome, difficulty speaking, decreased appetite, low activity of the thyroid gland, rash, liver damage, cough, pain in the abdomen and headache.

because these may affect the way the medications work.

Your doctor can discuss with you the possible side effects of the medications available to you. The tables in this guide list the main types of medications used to treat metastatic RCC along with their most common side effects.

How are RCC medications sequenced?

If you choose to have RCC medication to treat the cancer, you will be started on one medication or a combination of medications. This will be your first-line treatment. Clinical guidelines in the UK specify which medications are approved as first-line treatments, based upon evidence from clinical trials. Please see [Kidney cancer medicines](#) on our website for a list of currently available medications for RCC.

If the first medication doesn't work, causes side effects that you can't tolerate, or stops working, you may be offered a different type of medication. This is known as a second-line treatment. You could have a number of lines of treatment if you don't get on with your first or second treatment. Some

medications are only approved for first-line treatment, while others are only approved for second-line treatment or beyond. Your oncologist will talk through with you and explain the sequence of treatments available to you.

Access to medicines for RCC

All of the medications listed in this guide are licensed in the UK for the treatment of people with advanced kidney cancer. However, not all are available in NHS hospitals. Your oncologist will give you advice on the best treatment for you as a first-line treatment and for subsequent treatments that are funded by the NHS.

To access treatments that are not available in NHS hospitals, you might need to apply to government funding schemes, such as the Cancer Drugs Fund or your oncologist may submit an Individual Funding Request. Or you could pay privately for the medication that you need. You can also access treatments not available within the NHS by taking part in a clinical trial (for more information see Essential guide: *Clinical trials*). Please see [Access to medicines not available on the NHS](#) on our website for more information.



What are biomarkers?

A biomarker is a substance in the body that doctors can measure, to help them tell how a disease is developing or how well a treatment is working. Biomarkers can also be used for screening programmes for various types of cancer. So far, a reliable biomarker for kidney cancer has not been found. Clinical trials are ongoing to search for kidney cancer biomarker in urine, blood, breath and tissue samples.

Radiotherapy for advanced RCC

Radiotherapy uses high energy X-rays to destroy cancer cells. For patients who are unable to have surgery, it can be used to shrink tumours and so control symptoms. It can also be used if the cancer has spread to other areas of the body, such as the brain, lungs, liver or bone, or for the treatment of cancer that has come back.

Because kidney cancer cells are not very sensitive to radiation, radiotherapy is not used very often to treat kidney cancer patients. Radiotherapy may be used to help control pain and alleviate the symptoms of advanced RCC. It can be used to shrink a large tumour and relieve pressure on nearby organs, and the subsequent pain and discomfort this causes. Shrinking the tumour may also relieve the pressure on nerves that may be causing pain (neuropathic pain).

Treatment is given in the hospital radiotherapy department and will be tailored to you. Some people have daily treatments (or fractions) from Monday to Friday for several weeks. Some people may need only one or two treatment fractions. The treatment only takes a few minutes and does not hurt. You will be able to talk to the radiographer via an intercom if you need them.

Radiotherapy for kidney cancer that has spread

Radiotherapy can be very successful at controlling symptoms and slowing down the growth of the cancer if it has spread to your brain. It can be given in a number of different ways and is usually given in combination with steroids. How it is given depends mostly on the size and number of areas of cancer spread in the brain. If there are a few metastases in the brain, they may be treated with stereotactic radiotherapy (also called radiosurgery or gamma knife surgery or CyberKnife®). This uses high doses of radiation directed at the cancer using a head frame. Only a single treatment is required. If the cancer is widespread, there is the possibility of the spread of cancer cells throughout the brain, which are too small to detect on a scan. In this case, whole brain radiotherapy is sometimes used.

Stereotactic body radiotherapy (SBRT) can also be used to treat metastases found in the liver, lung and pancreas, as well as the brain. In SBRT, radiotherapy is directed at the area of the body containing the tumour so as to kill the cancer cells and avoid damaging as much healthy tissue as possible.

Side effects to radiotherapy can include fatigue, nausea and vomiting, and sore or red skin. They take a while to build up and usually persist for a few days after the treatment has finished. Your radiographer will be able to tell you what to expect and how to cope.

Further reading

- **Action Kidney Cancer:**
<https://www.actionkidneycancer.org>
- **Cancer Research UK:**
<https://www.cancerresearchuk.org/about-cancer/kidney-cancer/advanced/targeted-immunotherapy>
- **Macmillan:**
<https://www.macmillan.org.uk/cancer-information-and-support/kidney-cancer>
- **NHS:**
<https://www.nhs.uk/conditions/kidney-cancer/treatment/>

European Association of Urology (EAU) Renal Cell Carcinoma guidelines, 7. Disease management. <https://uroweb.org/guideline/renal-cell-carcinoma/#7>

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