

Understanding Your Treatment for Advanced Renal Cell Carcinoma (RCC)

I have just been diagnosed with advanced/metastatic RCC (kidney cancer). Are there any treatments for me?

There are 2 types of treatments for advanced/metastatic RCC: targeted therapies and immunotherapies.

- Targeted therapies act by either blocking the growth of new blood vessels that feed the tumor or by blocking important cellular proteins that help the tumor grow and survive. Examples of targeted therapies include: bevacizumab, axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and temsirolimus, or everolimus.
- Immunotherapies act by boosting a person's immune system by "releasing the brake" on the immune (T-cells) cells, so that these cells can attack the cancer cells and kill them. Examples of immunotherapies include: nivolumab alone or in combination with another immunotherapy treatment, ipilimumab. Pembrolizumab and avelumab are 2 immunotherapies that were recently approved to be given in combination with axitinib, a targeted therapy.

For some patients with a (favorable) prognosis, a targeted therapy is usually given at first, by itself. If that targeted therapy is not effective, another targeted therapy is given (or more commonly now, immunotherapy is given). In the United States and other western countries, regulatory agencies have recently approved a combination of 2 immunotherapies and 2 combinations using an immunotherapy, plus a targeted therapy.

Older immunotherapies include specific cytokines (proteins that boost someone's overall immune system), not just to treat cancer or a specific type of cancer. Examples of these types of cytokines include: interleukin-2 and interferon alfa.

The specific drugs in each of these categories may not be available in every country, so you will need to ask your doctor which drugs are approved for use in your country. Also, some countries allow you to pay cash for these medications, even if they are not covered by a government healthcare plan.

Tell me more about immunotherapies. How are they going to treat my RCC?

Immunotherapies act by boosting a person's immune system. One of the key components of our immune systems are checkpoints, which are specific proteins on immune cells that need to be turned off for an immune response to start. These checkpoints are "the brakes" for our immune system. Immunotherapies for RCC include checkpoint inhibitors, which release the brakes of immune cells and allow them to create an immune response against cancer cells.

Some checkpoint inhibitors block a protein called PD-1, which resides on T cells. Blocking PD-1 turns off the checkpoint and allows the T cells to attack a tumor. PD-1 inhibitors can help to shrink a tumor or slow its growth. Examples of PD-1 blockers are nivolumab and pembrolizumab.

Another checkpoint is called PD-L1. Again, blocking PD-L1 releases the brake and allows the T cell to start an immune response against a tumor. Avelumab is a PD-L1 blocker.

Finally, CTLA4 is another protein that acts as a checkpoint, so blocking it helps to boost an immune response. Ipilimumab is a CTLA4 blocker.

Older immunotherapies also include cytokines, which are proteins that boost the immune system overall, not just to treat cancer or a specific type of cancer. They are effective at shrinking the tumor, but they come with some serious side-effects, so these types of therapies are usually reserved for people who are healthy enough to tolerate them and did not respond well to targeted therapies or immunotherapies.

What is targeted therapy, and how is it going to treat my RCC?

Targeted therapies for RCC act in 2 ways: first, they block the formation of blood vessels that feed the tumor or block important cellular proteins that help the tumor grow and survive. Tumors are like any other human tissue; they need blood vessels to stay healthy and keep growing. Targeted therapies can block the growth of blood vessels in the immediate direct area of the tumor (its microenvironment), thus starving the tumor of important nutrients.

The second type of targeted therapy blocks the protein mTOR (which stands for mammalian target of rapamycin) that controls cell growth and metabolism. These drugs are called mTOR inhibitors.

Will my treatment for RCC have side-effects? What are they? How can I manage them?

All cancer treatments have side-effects; they vary by the specific drug. But, generally speaking, the main side-effects of targeted therapies that affect blood vessel growth include high blood

pressure, blood clots, diarrhea, nausea, fatigue, inflammation of the mouth and lips (stomatitis), hand-foot skin reactions, liver function problems, rash, and hoarseness of voice. Other side-effects of mTOR inhibitors include fatigue, anemia, stomatitis, and metabolic syndrome, which may lead to increased blood sugar and/or cholesterol and triglycerides. Weight loss is another adverse event. For patients who experience most of these side-effects, the targeted therapy is stopped temporarily to let the symptoms reduce or resolve, and then the targeted therapy is resumed at a lower dose.

For checkpoint inhibitors, the main side-effects include organ inflammation, inflammation of the lung, pituitary gland, colon, liver, skin, or kidney. These side-effects are considered to be “immune related” and are treated with either corticosteroids (to reduce inflammation) or another drug, that can dampen the immune response. If the side-effect is considered serious or life threatening, immunotherapy treatment may be delayed for several weeks or permanently discontinued.

What happens if my treatment stops working?

Fortunately, there are many treatments available for patients with kidney cancer and more are in development. If one treatment stops working, doctors will usually try a different drug with a different mechanism of action. Some treatments are now approved to give as combinations.

What is a clinical trial? Are there any for people with RCC?

Clinical trials are studies of new drugs in patients with a particular disease. The studies occur in 4 phases:

- **Phase I** studies are usually performed in patients with different cancers with the goal of finding out if an agent/drug is safe for humans when given at a certain dose and schedule. These studies also try to determine if that agent/drug at a particular dose and schedule shows clinical activity is beneficial for patients. This therapy can be tested later in patients with a specific type of cancer, where the results from the phase I trial show efficacy more in patients with a specific tumor type. The purpose of phase I studies is to observe the basic safety and tolerability of the agent/drug.
- **Phase II** studies are performed in patients with one specific tumor, and the goal of these studies is to determine the efficacy and side-effects of a particular therapy when given at the dose and schedule that was recommended from the phase I study.

- Phase III studies use the optimal dose in selected patients and are carefully designed to measure efficacy and safety, either compared to a placebo or to the current standard drug/treatment that is usually given. These studies are usually the ones that, if successful, will lead to approval by a regulatory agency of a particular therapy for use in the general population of patients with a particular type of cancer.
- Phase IV studies are performed once a drug is approved for use; they help to clarify the efficacy, safety, and cost of the drug in the “real world” (ie, not in a carefully controlled scientific setting).

There are numerous clinical trials underway for patients with RCC. Be sure to discuss this with your physician if you are interested in participating in one.