What is immunotherapy?
This is a type of cancer drug treatment that focuses on using the body’s own immune system to fight cancer.

How immunotherapy works
Different types of immunotherapy work in several different ways. Immunotherapy can:
• boost the immune system so it works better against cancer
• remove barriers to the immune system attacking the cancer.

About the immune system
The immune system protects the body from infections. It’s made up of a network of cells and organs including the tonsils, lymph nodes, appendix, thymus, spleen and bone marrow. When a foreign organism such as a germ enters the body, the immune system recognises and then attacks it, so that it doesn’t harm the body. This process is called an immune response.

White blood cells called lymphocytes are part of the immune system. They are produced in the bone marrow. There are two main types of lymphocytes:

B-cells – fight bacteria and viruses by making proteins called antibodies. The antibody locks onto the surface of the invading bacteria or virus.

T-cells – help control the immune system, assist B-cells to make antibodies, and may attack abnormal cells.

Cancer and the immune system
The immune system’s ability to detect and destroy abnormal cells usually prevents cancers from developing. However, some cancer cells find ways to stop the immune system destroying them. The natural immune response to cancer cells may not be strong enough to fight them off. Also, cancer cells can change over time (mutate) and then escape from the immune response.
Understanding Immunotherapy

**Types of immunotherapy**

Immunotherapy can trigger the immune system to fight cancer in different ways.

**Immunotherapy available now**

**Checkpoint inhibitors** – On the surface of T-cells are proteins called “checkpoints” that stop the immune system from attacking cancer cells.

Drugs called checkpoint inhibitors block certain proteins so the T-cells can recognise and destroy cancer cells.

The checkpoint inhibitors that are currently available can block the following proteins:
- Programmed death-1 (PD-1)
- Programmed death-ligand 1 (PD-L1)
- Cytotoxic T-lymphocyte-associated antigen (CTLA-4).

Checkpoint inhibitors are now the most widely used form of immunotherapy. The types currently subsidised by the Australian Government through the Pharmaceutical Benefits Scheme (PBS) include pembrolizumab (Keytruda), nivolumab (Opdivo) and ipilimumab (Yervoy). These drugs are approved and reimbursed for people with advanced melanoma. Nivolumab has recently been approved and will soon be reimbursed for kidney and lung cancers.

They are also being tested for other cancers, and may soon be approved and reimbursed for cancers of the head and neck, and bladder.

**Immune stimulants** – Some treatments have been used to stimulate the immune system so it reactivates and attacks the cancer.

Examples include:

- In non-muscle-invasive bladder cancer, the vaccine Bacillus Calmette-Guérin (BCG) is given into the bladder through a catheter to stimulate a person’s immune system to stop or delay bladder cancer coming back or becoming invasive.

- In some types of skin cancers, a cream called imiquimod is applied directly to the affected area to stimulate a local immune response.

**Immunotherapy in clinical trials**

**Adoptive cell transfer** – This boosts the ability of the body’s T-cells to fight cancer.

Chimeric antigen receptor (CAR) T-cell therapy is a type of adoptive cell transfer that is showing benefits for some people with some types of leukaemia and lymphoma.

First, T-cells are removed from the blood and a new gene is introduced into the cells to enable them to recognise cancer. The T-cells are then returned to the blood by an intravenous drip (infusion). The altered T-cells multiply and trigger a number of immune responses that attack the cancer cells.

**Cytokines (immune hormones)** – These are proteins made by white blood cells that stimulate the immune system.

The two main types of cytokines that have been used to treat cancer are interferons, which help the immune system to slow the growth of cancer cells, and interleukins, which stimulate anti-cancer T-cells.

Interferons were once used at high doses to help people with melanoma and kidney cancer, but they were found to be toxic. They are currently being trialled at lower doses and given with checkpoint inhibitors. If these trials are successful, interferons may be used to treat cancer in the future.

**Oncolytic viruses** – These viruses directly infect tumour cells and cause an immune response against the infected cells.

**Other immune treatments**

Vaccines help train the immune system to prevent cancer. There are prevention and treatment vaccines, but treatment vaccines have not been successful.

The human papillomavirus (HPV) vaccine is used to prevent cervical cancer, and it is hoped it will also prevent penile and anal cancers and some cancers of the head and neck. Vaccines against hepatitis B and hepatitis C viruses help prevent liver cancer.
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How is immunotherapy different from other cancer treatments?

As well as immunotherapy, treatments for cancer include:

**Surgery** – removes cancer from a specific area of the body. It is common to have some pain after surgery. You’ll be given advice on how to prevent infection during recovery.

**Radiotherapy** – uses high-energy x-rays to kill or damage cancer cells to target a specific area of the body. This can cause side effects at or near the treatment site.

**Chemotherapy** – uses drugs to kill or damage rapidly dividing cells anywhere in the body. This means most chemotherapy drugs harm cancer cells as well as healthy cells. This can cause side effects such as nausea, fatigue and hair loss. It can also lower the immune system by reducing white blood cell counts.

**Targeted therapy** – focuses on proteins or mutations found in some tumours. These drugs attack specific targets inside tumours that are causing the tumour to grow uncontrollably. While it is generally more precise than chemotherapy, targeted therapy can cause significant side effects.

As researchers learn more about cancer, treatment changes. Immunotherapy is not a new idea, but earlier strategies were less effective. Checkpoint immunotherapy is having more positive results.

Like all treatments, checkpoint immunotherapy can cause side effects. Because checkpoint immunotherapy acts on the immune system, it can cause inflammation in any part of your body. This can lead to a variety of side effects such as skin rash, diarrhoea and breathing problems.

Who may benefit from immunotherapy

Immunotherapy is not yet as widely used as surgery, chemotherapy and radiotherapy. However, checkpoint immunotherapy is likely to benefit some people with some types of cancer.

In Australia, it has been used in clinical trials for cancers in the head and neck, bladder, kidney, lung, as well as melanoma, leukaemia and lymphoma. Immunotherapy is being studied for use in many other types of cancer.

To date, most people who’ve had immunotherapy have had advanced cancer. Their cancer has either recurred and spread after primary treatment, or they were first diagnosed at an advanced stage.

Immunotherapy is not right for everyone, so talk to your doctor to find out whether you may benefit from this treatment. Most studies show that immunotherapy is more likely to work for people who have few, if any symptoms from their cancer.

To work out if immunotherapy is suitable, doctors will consider:
- your overall health
- the type and stage of cancer
- your treatment history.

How immunotherapy is given

Checkpoint immunotherapy is usually given directly into a vein (intravenously).

How often and how long you have immunotherapy depends on:
- the type of cancer and how advanced it is
- the type of immunotherapy you get
- how you respond to treatment and the side effects, if any, you experience from treatment.

Sometimes two immunotherapy drugs are given together. You may have treatment every 2–3 weeks in a repeating cycle, with each period of treatment followed by a rest period.

Immunotherapy drugs seem to keep working for varying periods of time, because they act directly on the body’s own immune system. They sometimes keep working even long after treatment stops.
Understanding Immunotherapy

The challenges of immunotherapy
You may have several questions and concerns about having immunotherapy. There have been media reports of how immunotherapy is a “miracle drug” and how it can cure cancer. Some people, especially with advanced melanoma, have had encouraging outcomes. Because of these factors, people’s expectations can be high when starting treatment.

Will it work? – The most challenging issue is that checkpoint immunotherapy doesn’t work for everyone – only a small number of people respond well to immunotherapy. The percentage is higher for some cancers such as melanoma. To make the benefits of immunotherapy available to more people in the future, researchers are trying to understand why some people respond better than others.

How long will it take to work? – As most checkpoint immunotherapy takes a while to work, people and their families may experience anxiety waiting to see whether they’ll respond to the treatment. And if it does work, some people are always wondering how long immunotherapy will control the cancer or whether the cancer will come back. Let your nurse or doctor know how you’re feeling. They may recommend you see a psychologist to work through your thoughts. For more information on coping with uncertainty, read Cancer Council’s Emotions and Cancer booklet.

How much will it cost? – The cost of checkpoint immunotherapy is high. As of June 2017, only treatment for melanoma is reimbursed by the PBS, but reimbursement for kidney and lung cancers is expected soon.

Some immunotherapy drugs may be available through clinical trials or, sometimes, through a compassionate access program. To access immunotherapy for cancers that are not currently reimbursed, some people choose to make significant financial decisions to cover the costs. Before considering paying for these drugs, ask your doctor for details about the benefits of immunotherapy for your type of cancer.

Side effects
The side effects of checkpoint immunotherapy are different from other cancer treatments. Not everyone will experience the same side effects, and some people may have no side effects. The side effects can vary depending on the type of immunotherapy you receive and how your body responds.

Since your immune system takes care of your whole body, immunotherapy can cause inflammation in any of the organs in the body. This can mean that some people with an autoimmune disease such as lupus or rheumatoid arthritis may find it difficult to have immunotherapy safely. Discuss this with your doctor if you have an autoimmune disease.

Common side effects include fatigue, skin rash and diarrhoea – which can vary in severity and duration.

Side effects are likely to be more severe if you are taking a combination of immunotherapy drugs or having immunotherapy with other cancer treatments.

Let your doctor know about side effects
As immunotherapy works differently from other cancer treatments, it’s important to work closely with your doctor to monitor your response.

Before immunotherapy starts, discuss the specific side effects you may experience with your doctor. Ask your doctor or nurse which side effects to watch out for or report, and who to contact after hours.

During treatment, let your medical team know about any side effects you experience. Side effects can be better managed when they are reported early. If they are not treated, side effects may become serious, and treatment may need to be stopped until the side effects are better controlled. Occasionally, immunotherapy must be stopped permanently if the side effects are too severe.
Understanding Immunotherapy

Side effects of immunotherapy
Some side effects are common and some are more rare. Examples of both are shown below.

**Common side effects**

- **Dry irritated eyes**
  Could be inflammation of the eyes or inflammation of the tear glands

- **Pain in the joints**
  Could be a sign of inflammation of the joint (arthralgia)

- **Diarrhoea, bloody stools, abdominal pain and bloating**
  Could be signs of inflammation of the bowel (colitis)

- **Skin rashes on the body**
  Could be signs of dermatitis, which makes skin itchy and appear red and bumpy

**Rare side effects**

- **Headache, change in vision**
  Could be signs of inflammation of the pituitary gland (hypophysitis)

- **Thyroid-related issues**
  Could be signs of the thyroid working too fast (weight loss, feeling warm) or the thyroid working too slow (weight gain, feeling cold)

- **Shortness of breath and coughing**
  Could be signs of inflammation of the lungs (pneumonitis)

- **Yellowing of the eyes, severe abdominal pain and dark urine**
  Could be signs of inflammation of the liver (hepatitis)

Managing the side effects of immunotherapy

Side effects can sometimes begin within days of starting treatment, but more commonly they occur weeks or even months after starting treatment.

In some rare cases, they can occur after treatment has ended. Work with your doctor to develop a plan for how long to look out for potential side effects.

To manage the side effects, it is important to let your health care team know about new symptoms. Even if you are experiencing side effects, you can continue to benefit from immunotherapy.

Side effects will be graded to help decide how to treat them.

**Moderate and severe side effects** – These are often treated with steroids such as prednisone.

**Severe side effects** – In some cases, people may need to be hospitalised or treated with high doses of steroids if side effects are severe. Side effects often improve with treatment, but sometimes they can be serious and people will be unable to continue immunotherapy.

How will I know whether the immunotherapy is working?

You will have regular check-ups with your doctor, blood tests and different types of scans to check whether the cancer has responded to treatment.

It may take some time to know whether immunotherapy has worked because some people have a delayed response. Occasionally, people may see their cancer get worse before improving.

A good response from immunotherapy will make the cancer shrink. In some cases, the cancer remains stable, which means it doesn’t increase in size on scans but also does not decrease or disappear. People with stable disease can continue to have a good quality of life.
How do I access immunotherapy treatment?
Ask your doctor if immunotherapy is a suitable treatment for you. Only checkpoint immunotherapy for advanced melanoma is currently approved and reimbursed through the PBS in Australia. Immunotherapy for advanced kidney cancer and lung cancer is approved, and will probably be reimbursed in the near future.

For other cancers, it may be possible to access immunotherapy treatments through clinical trials. Speak with your treatment team for more information, and ask if you’re able to join a clinical trial. Call Cancer Council 13 11 20 for a free copy of Understanding Clinical Trials and Research.

Question checklist
• Is immunotherapy available as part of my treatment plan. If not, why not?
• What do you expect the immunotherapy to do to the cancer?
• Which immunotherapy are you recommending?
• Will it be my only treatment, or will I also have other treatments?
• How often will I receive immunotherapy? How long will I have treatment?
• Where will I have treatment?
• What side effects should I watch out for or report?
• Who do I contact if I get side effects?
• How can side effects be managed?
• What immunotherapy clinical trials are available?
• How will I know if the treatment is working?
• How much will immunotherapy cost?
• Can I take immunotherapy with my other medicines? What about the flu vaccine?

Useful websites
The internet has many useful resources, although not all websites are reliable. The websites listed below are good sources of information.

- American Cancer Society cancer.org
- Cancer Research Institute cancerresearch.org
- European Cancer Patient Coalition (ECPC) Immuno Oncology portal iop.ecpc.org
- Society for Immunotherapy of Cancer (SITC) sitcancer.org
- Understanding immuno-oncology for kidney cancer 10forio.info

Where to get help and information
Call Cancer Council 13 11 20 for more information about immunotherapy. Trained health professionals can listen to your concerns, provide information, and put you in touch with local services and support groups. Ask for free copies of booklets that may be relevant to you, or download digital versions from your local Cancer Council website:

- ACT ................................................ actcancer.org
- NSW ........................................ cancercouncil.com.au
- NT ............................................. nt.cancer.org.au
- QLD ........................................... cancerqld.org.au
- SA ............................................. cancersa.org.au
- TAS ............................................. canceritas.org.au
- VIC ............................................. cancervic.org.au
- WA ............................................. cancerwa.asn.au
- Australia ......................................... cancer.org.au

Acknowledgements
This information was reviewed by: Dr Craig Gedye, Medical Oncologist, Calvary Mater Hospital, Newcastle, and Conjoint Senior Lecturer, School of Biomedical Sciences and Pharmacy, The University of Newcastle, NSW; Dawn Bedwell, 13 11 20 Consultant, Cancer Council Queensland, QLD; Prof Michael Brown, Director, Cancer Clinical Trials Unit, Royal Adelaide Hospital, SA; Christine Maxwell, Consumer; Julie Teraci, Clinical Nurse Consultant, Western Australian Melanoma Advisory Service, St John of God Subiaco Hospital, WA; Helen Westman, Immuno-Oncology Cancer Nurse Coordinator, Royal North Shore Hospital, NSW.

Note to reader
Always consult your doctor about matters that affect your health. This fact sheet is intended as a general introduction and is not a substitute for professional medical, legal or financial advice. Information about cancer is constantly being updated and revised by the medical and research communities. While all care is taken to ensure accuracy at the time of publication, Cancer Council Australia and its members exclude all liability for any injury, loss or damage incurred by use of or reliance on the information provided in this fact sheet.