Keytruda benefits a small proportion of men with late-stage metastatic prostate cancer.

Dec 2019, Wendy Winnall, scientific writer for PCFA

Keytruda is an immunotherapy drug that has revolutionised treatment for cancers such as melanoma and lung cancer. Unfortunately, the same level of success has not been seen for prostate cancer. Now a new study has some hopeful results, showing a small proportion of men with late-stage prostate cancer will benefit from Keytruda.

In May 2017, the US Food and Drug Administration (FDA) for the first time approved a cancer treatment based on a common biomarker, rather than the location in the body where the tumour originated. The drug, Keytruda (Pembrolizumab), was approved for use by patients who have tumours carrying a genetic defect that makes them susceptible to the drug. Keytruda is a very successful cancer drug that is now used to treat many different types of cancer in Australia.

How does Keytruda work?
Prostate cancers and other types of tumours change the normal cells in the body. Some tumours protect themselves by stopping immune responses. They make inhibitors that stop immune cells from attacking the tumour cells. Keytruda reverses some of these changes, allowing the immune system to join the fight against the tumour. Two other immunotherapy drugs work using similar methods; Opdivo (Nivolumumab) and Yervoy (Ipilimumab). For some cancers these immunotherapies make a big difference, reducing tumour growth for many years. But the downside to this treatment is that the immune cells are more likely to attack normal cells, leading to side effects.

Keytruda is called a checkpoint blockade inhibitor. It targets proteins called PD-1 receptors on the surface of immune cells. This receptor is responsible for stopping the immune system from fighting against the body’s own cells. Tumours make inhibitors that bind to this receptor, shutting down all immune responses from the cells with PD-1 receptors. By stopping this happening, Keytruda makes it easier for the immune cells to recognise cancer cells and fight against them.

The Keynote-199 study
A new clinical study has asked whether Keytruda helps men with late-stage prostate cancer. The researchers behind this study are a large international team, led by Prof Johann de Bono from the Institute of Cancer Research and Royal Marsden Hospital in London. This study tracked the experiences of men with metastatic tumours taking Keytruda. These men already had treatment for their metastatic cancer and were running out of options.

Men volunteering for the trial were classified into 5 different groups, called cohorts. First results have recently been published for 3 of these groups. Each group consisted of men with metastatic castration resistant prostate cancer – tumours that has spread to distant sites and were no longer controlled by hormone therapy. They had previous chemotherapy, as well as Enzalutamide (Xtandi) and/or Abiraterone (Zytiga).

**Cohort 1** (133 men): tumours samples showed the presence of PD-1 inhibitors. These men might be more likely to benefit from Keytruda.

**Cohort 2** (66 men): tumour samples did not show inhibitors of PD-1.

**Cohort 3** (59 men): had multiple tumours in their bones. Samples to test for PD-1 inhibitors were unavailable.

Men in each group had Keytruda treatment once every 3 weeks. Treatment continued until their tumours started growing, or they decided to stop due to other reasons such as side effects.

The main read-out for this study was response to treatment. This was defined as a reduction of tumour size seen on scans. The researchers also asked how long the men lived, whether their disease was stabilised and what were the side effects from treatment. Stabilisation of prostate cancer means no growth in the tumours, but not a reduction in size.

**Cohort 1**: 5% of men saw their tumour size decrease on scans. This was 7 out of 133 men. A further 10% had their disease stabilise with Keytruda treatment. The overall average survival time was 9.5 months after Keytruda treatment started.

**Cohort 2**: 3% of these men benefitted from a decrease in tumour size and 9% in stabilised disease. Their average survival time was 7.9 months.

**Cohort 3**: 22% of these men had a stabilisation in their disease. None of these men had a reduction in tumour size, but one had a considerable reduction in PSA. Their average survival time was 14.1 months after treatment began.
To summarise, only a small proportion of men with late-stage metastatic prostate cancer saw a reduction in tumour size, and 9% to 22% of men saw their disease stabilise for a period of time. The men who had a reduction in tumour size had long-lasting responses.

Side effects from treatment
As for all cancer therapies, many of these men experienced side effects. These included tiredness, diarrhoea, low appetite, nausea and many more. Not every man experienced these side effects. The most common was tiredness in 15% of men. Some side effects were likely caused by the increase in immune reactions due to Keytruda treatment. The more serious of these were colitis (inflammation of the large intestine) in 2% of men and skin rash in 2% of men.

Conclusions from this study
A small proportion of men with late-stage metastatic prostate cancer benefited from Keytruda in this study. Men who did benefit saw their cancer growth slowed for a considerable period of time. It will take time and more research to work out how to best translate these promising results to the Australian community. Randomised controlled trials (the gold standard trial type) need to be done to more precisely determine who would benefit from Keytruda for prostate cancer.

This study has a few drawbacks. It had no control group for comparisons. So we don’t know the equivalent rates of response, survival and stable disease for similar men who had no Keytruda. It was also a fairly short-term study. However, the survival times and responses seen for some men were encouraging. The researchers concluded that Keytruda had anti-tumour activity for some men. They hope that a biomarker can be found to help identify the men most likely to benefit from this drug. The Keynote-199 study continues to follow-up on these and other men to detect promising uses for Keytruda by men with late-stage prostate cancer.

It is possible for some Australian prostate cancer patients to receive Keytruda (Pembrolizumab). Men with castration resistant prostate cancer, whose genetic tests indicate specific mutations are present, can access this drug once they have tried other treatments. These are only about 2 to 3% of men with advanced prostate cancer, and specific requirements must be met.