

# Enzalutamide has benefits when taken after Abiraterone by men with metastatic prostate cancer.

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Two anti-hormone drugs are available in Australia to treat metastatic prostate cancer. Both Abiraterone and Enzalutamide can slow the growth of these tumours. A new clinical trial has asked whether men would benefit from taking one after the other, and which order is best.

The most dangerous type of prostate cancer is the stage where tumours have spread to distant sites and are no longer stopped by hormone therapy. This is called metastatic castration resistant prostate cancer. Australian men with this late stage of prostate cancer have a choice of two anti-hormone drugs to take: Abiraterone or Enzalutamide.

Unfortunately, prostate cancer has a nasty habit of becoming resistant to these drugs. It would be useful to know whether one will work after the other stops working, and which is the best order to take them.

## **First and second-line hormone therapy**

Hormone therapy (androgen deprivation therapy, ADT) involves numerous different drugs that reduce the production of testosterone. It's a very useful treatment for prostate tumours because prostate cancer cells usually rely on testosterone to grow. Hormone therapy is used by most men with advanced prostate cancer, as well as men with intermediate or high-risk localised cancer together with radiotherapy. Some men choose surgery to remove their testicles (called surgical castration). Unfortunately, both hormone therapy and castration surgery are not always enough to stop advanced prostate cancer from growing and spreading. One reason for this is that the tumours themselves start producing their own testosterone.

Prostate cancer that is resistant to initial hormone therapy can be treated using drugs known as second-line hormone therapy. Second-line anti-hormone drugs available in Australia include Abiraterone (Zytiga) and Enzalutamide (Xtandi). Apalutamide is another second-line anti-hormone drug. It's approved for men whose PSA is rising despite first-line hormone

therapy, but who have no tumours visible on scans. Unfortunately, Apalutamide is not subsidised for this purpose in Australia, so its use is very expensive.

### **Abiraterone (Zytiga)**

*What it does:* Abiraterone is an inhibitor of testosterone production. Abiraterone mimics testosterone. It binds to receptors and enzymes where testosterone would normally be. This inhibits both the production of testosterone and the ability of testosterone to promote tumour growth.

*Who can take it?* Abiraterone acetate is taken in combination with the anti-inflammatory drugs prednisone or prednisolone. In Australia, the TGA has approved Abiraterone for men with:

- newly diagnosed high-risk metastatic prostate cancer in combination with hormone therapy, or...
- metastatic castration resistant prostate cancer once hormone therapy fails to control their cancer, or...
- metastatic castration resistant prostate cancer who have received prior chemotherapy (docetaxel (Taxotere) or cabazitaxel (Jevtana)).

*What are the possible side effects?* The most common side effects from Abiraterone are diarrhoea, fluid in legs and feet, low blood potassium, urinary tract infection, high blood pressure and bone fractures. Rarer side effects include heart failure, blood in urine and numerous other issues. Full details available at this [link](#).

### **Enzalutamide (Xtandi)**

*What it does:* Enzalutamide slows tumour growth by stopping male hormones from binding to androgen receptor proteins on the surface of prostate cancer cells.

*Who can take it?* The TGA has approved Enzalutamide for use by men with:

- non-metastatic castration-resistant prostate cancer (whose PSA is rising despite hormone therapy, but no metastatic tumours are seen on scans), or...
- metastatic castration resistant prostate cancer that is no longer held back by hormone therapy, but chemotherapy is not yet suitable, or...
- metastatic castration resistant prostate cancer after having chemotherapy (docetaxel (Taxotere)).

*What are the possible side effects?* The most common side effects are fatigue, nausea, hot flushes, diarrhoea, fatigue, high blood pressure and fractures. Other important side effects include seizures, difficulty thinking clearly, low levels of some blood cells and falls. There are numerous other potential issues, with full details available at this [link](#).

There are long lists of potential side effects from these drugs. But not every issue is experienced by each man taking these drugs. Your doctor can discuss which drug is most suitable for you and help with managing the side effects.

### **Which is best?**

Both Abiraterone and Enzalutamide can be taken by men with metastatic castration resistant prostate cancer. It's difficult to say which one is the best. The reasons for this is that the two drugs haven't been directly compared against each other in a clinical trial. The two drugs have very similar benefits for men at the late stage of prostate cancer, leading to increased survival times and increasing the time until PSA levels rise. Both have the risk of side effects, with differing types of side effects. Depending on the expected side effects and existing health issues, doctors can make recommendations on which is most appropriate for individuals. Unfortunately, prostate cancer inevitably becomes resistant to these drugs.

### **A new Canadian cross-over trial**

A new study from Canada has asked if there is an optimal sequence for taking these two drugs. In other words, would taking one first, then the other, extend the time until PSA levels rise? Which is the best order? The team leader was Dr Kim Nguyen Chi from BC Cancer in Vancouver, British Columbia. The results from their study have recently been published in the journal [Lancet Oncology](#).

The Canadian trial was a randomised, phase 2 trial. Men joining the trial knew which drugs they were having (meaning that it wasn't "blinded"). This trial used a *cross-over* design. Men in group A took Abiraterone first, then Enzalutamide, once the Abiraterone no longer worked. They were compared to men in group B, who took Enzalutamide first, then Abiraterone. There were 101 men who were randomly assigned into each group.

Men joining this trial had metastatic castration resistant prostate cancer. Their disease had spread to distant sites and their PSA levels were rising despite hormone therapy. Most had tumours in their bones and some had tumours in their lungs or liver. Most of these men had not been treated with chemotherapy.

Results for group A were better than for group B. In other words, **men having Abiraterone first then Enzalutamide second had better outcomes**. It was an average of 19.3 months before their PSA rose, compared to 15.2 months for men having Abiraterone second.

Enzalutamide worked for some men when taken second, but Abiraterone rarely did so. 36% of the men having Enzalutamide second saw their PSA decline. But only 4% of men taking Abiraterone second had a decline in their PSA levels. The researchers predict that the better outcomes for group A are due to Enzalutamide working after Abiraterone, whereas Abiraterone does not seem to help when used second.

As expected, most of the men suffered from treatment side effects. Common serious side effects were high blood pressure and fatigue. Fortunately, the proportion of men experiencing serious side effects in group A was no higher than in group B. In group A (Enzalutamide second), 15% of men suffered from some type of serious side effect, compared to 20% in group B (Abiraterone second).

### **What does this mean for Australian men with advanced prostate cancer?**

This trial provides evidence that the optimal order of the two drugs is to take Abiraterone first then Enzalutamide. However, there are some limitations to the results. This is not a phase 3 trial, so the number of participants was relatively small. Survival times were not measured, just the time until PSA levels rose. So the level of evidence is not necessarily enough to change clinical guidelines.

Your doctors can help you decide which one of these drugs to take. There are some differences in the expected side effects and reasons why one may be more suitable than another. For example, Abiraterone may be a better option than Enzalutamide for men who have had falls or seizures. Alternatively, Enzalutamide might be better than Abiraterone for men whose tumours have spread to their liver or lungs. There are numerous health issues that will be taken into account by doctors before making a recommendation on which drug to start.