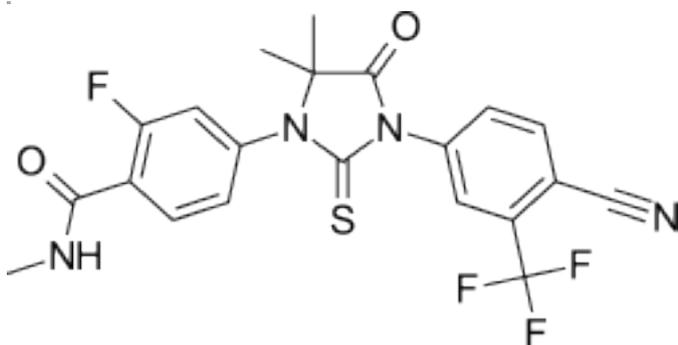


## Enzalutamide

**Enzalutamide** (marketed as **Xtandi** and formerly known as **MDV3100**) is an androgen receptor antagonist drug developed by the pharmaceutical company Medivation for the treatment of metastatic castration-resistant prostate cancer.<sup>[1]</sup> Medivation has reported up to an 89% decrease in prostate specific antigen serum levels after a month of taking the medicine.<sup>[2]</sup> Early preclinical studies also suggest that enzalutamide inhibits breast cancer cell growth.<sup>[3][4]</sup> In August 2012, the U.S. Food and Drug Administration approved enzalutamide for the treatment of castration- resistant prostate cancer.<sup>[5][6]</sup>

### Enzalutamide



### Systematic (IUPAC) name

4-(3-(4-Cyano- 3-(trifluoromethyl)phenyl)-5,5-dimethyl- 4-oxo-2-thioxoimidazolidin-1-yl)-2- fluoro-*N*-methylbenzamide

### Clinical data

**Trade names** Xtandi

**AHFS/Drugs.com entry**

**Licence data** US FDA:[link](#)

**Pregnancy cat.** X (US)

**Legal status** R-only

**Routes** (US) Oral

### Identifiers

CAS number 915087-33-1

ATC code None

PubChem CID 15951529

ChemSpider 13093347

UNII 93T0T9GKNU

ChEBI CHEBI:68534 ✓

## Chemical data

Formula **C<sub>21</sub>H<sub>16</sub>F<sub>4</sub>N<sub>4</sub>O<sub>2</sub>S**

Mol. mass 464.44 g/mol

SMILES

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## Discovery

Enzalutamide was discovered by Charles Sawyers who is now at Memorial Sloan–Kettering Cancer Center and Michael Jung at UCLA.<sup>[7][8]</sup>

## Preclinical pharmacology

Enzalutamide has approximately fivefold higher binding affinity for the androgen receptor (AR) compared to the antiandrogen bicalutamide.<sup>[9]</sup> As opposed to bicalutamide, enzalutamide does not promote translocation of AR to the nucleus and in addition prevents binding of AR to DNA and AR to coactivator proteins.<sup>[9]</sup>

When LNCaP cells (a prostate cancer cell line) engineered to express elevated levels of AR (as found in patients with advanced prostate cancer) were treated with enzalutamide, the expression of androgen dependent genes PSA and TMPRSS2 was down regulated in contrast to bicalutamide where the expression was upregulated.<sup>[9]</sup> In VCaP cells which over express androgen receptors, enzalutamide induced apoptosis whereas bicalutamide did not.

<sup>[9]</sup> Furthermore enzalutamide behaves as an antagonist of the W741C mutant androgen receptor in contrast to bicalutamide which behaves as a pure agonist when bound to the W741C mutant.<sup>[9]</sup>

Enzalutamide inhibits (in vitro) the estrogen receptor in breast cancer with a similar effectivity as tamoxifen in addition to blocking the androgen receptor of androgen receptor.<sup>[10]</sup>

## Clinical studies

Enzalutamide is clinically active in metastatic castration-resistant prostate cancer.<sup>[11]</sup> PSA level decreased more than 50 percent in 40/65 chemo-naive patients and 38/75

chemotherapy-treated patients.<sup>[11]</sup> Median time to radiographic progression was 56 weeks for chemo-naïve patients and 25 weeks for the post-chemotherapy population.<sup>[12]</sup>

Medivation conducted an international phase III trial that began in September 2009 known as AFFIRM. The aim of this trial was determine the safety and effectiveness of enzalutamide in patients who have previously failed chemotherapy treatment with docetaxel.<sup>[13]</sup> In November 2011, this trial was halted after an interim analysis revealed that patients given the drug lived for approximately 5 months longer than those taking placebo.<sup>[14]</sup> FDA approval was granted in August 2012.<sup>[5][15]</sup> Another phase III trial known as PREVAIL is investigating the effectiveness of enzalutamide with patients who have not yet received chemotherapy.<sup>[16]</sup> On October 22, 2011, Medivation and Astellas announced that the PREVAIL trial met both co-primary endpoints of overall survival, with a 30% reduction in the risk of death compared with placebo (hazard ratio = 0.7; 95% confidence interval, range of 0.59-0.83), and radiographic progression-free survival, with an 81% reduction in risk of radiographic progression of death compared with placebo (hazard ratio = 0.19); 95% confidence interval, 0.15-0.23).<sup>[17]</sup> In addition, a phase II trial began in March 2011 comparing enzalutamide with a commonly used anti-androgen, bicalutamide, in prostate cancer patients who have progressed while on LHRH analogue therapy (e.g., leuporelin) or surgical castration.<sup>[18][19]</sup>

### See also

Abiraterone

Galeterone

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Enzalutamide - Wikipedia, the free encyclopedia <http://en.wikipedia.org/wiki/Enzalutamide>

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<http://pharmastrategyblog.com/2013/02/making-a-difference-in-advanced-prostate-cancer-an-interview-with-bertrand-tombal.html/>

## **Making a difference in Advanced Prostate Cancer – an interview with Bertrand Tombal**

By [MaverickNY](#) on February 15, 2013

Since 2010, we have seen several technological advances in therapies for metastatic castration resistant prostate cancer (CRPC), leading Professor Bertrand Tombal (an Academic urologist in Brussels, Belgium) to describe 2011 as a Grand Cru year for CRPC at the European Society of Medical Oncology. One of the most promising therapies in this category was enzalutamide (Xtandi) from Medivation.

Enzalutamide is an anti-androgen receptor antagonist similar to bicalutamide, but differs in that it is a more potent inhibitor and has no agonist properties. Initially, it was approved by the FDA post chemotherapy but trials are currently ongoing in the pre-chemotherapy setting.

In patients with advanced prostate cancer with hormonally-sensitive disease, the treatment choices can be fairly stark – active surveillance (for low risk patients), surgery (for resectable disease), radiation (risk of long term side effects) and/or androgen deprivation therapy (ADT) for high risk patients with rising PSA. When ADT fails and PSA rises dramatically again, then men may receive an androgen receptor antagonist such as bicalutamide. An advantage of bicalutamide is that it avoids medical castration and has been shown to have a favourable safety profile compared to ADT.

ADT is useful for controlling PSA levels in high risk patients, but it is not without complications, as Prof Tombal discusses below and explains why there is a need for an alternative approach:

In US, however, ADT is more commonly used in high risk patients than bicalutamide.

The most obvious question though, is how might enzalutamide compare with bicalutamide in the advanced prostate cancer setting? To find out about progress here, I interviewed Prof Tombal about his poster being presented at the [ASCO Genitourinary meeting](#) yesterday.

**PSB: How would you describe the rationale behind your study?**

**Prof Tombal:** The first thing that is important is what is the philosophy of the clinical trial? There has been a lot of activity in medical treatment for prostate cancer with new drugs like abiraterone, Jevtana, new chemotherapies, a vaccine, but what they all have in common that they are used in patients who are failing hormonal treatment. Today, hormonal treatment worldwide is basically medical castration, meaning that you suppress the testosterone in the whole body to get an effect on the prostate and the metastases.

The idea was to test enzalutamide, not the way it is used and prescribed now in patients who fail androgen therapy, but in patients who have never received androgen deprivation therapy. There was always the hypothesis that it might not work for unknown reasons. **So we took patients who needed hormone therapy, some of them were already quite advanced, and we gave enzalutamide alone.**

**PSB: What kind of results did you see?**

We were extremely impressed by the amplitude of response of these men. If we look at the PSA decrease, when we did that hypothesis that if 80% of the men would have a good PSA response, we would potentially have a drug with some future in that setting. But it's not 80%, it's much more than that. **Almost all the men responded extremely profoundly to the drug with a sharp decrease in PSA, and with a toxicity that apparently is less pronounced than with androgen deprivation therapy.**

The hypothesis that we might have a drug that could eventually replace androgen deprivation therapy, we now we know that the idea seems to be working and we are now saying OK, now we might have a compound simply to replace androgen deprivation therapy in all these men who need it and suffer from side effects.

Now it is creating a new paradigm because now we have to think about how we are going to develop this in the next 4 to 5 years. What is striking with the result is that actually enzalutamide is the only drug you can use as an alternative. If you think, for instance, about Zytiga/abiraterone, it needs to be used with hormone therapy, it will never replace hormone therapy. Here it is a short series (of treatment) but you have to understand we went totally blind in that patient population.

What we can say about the results is that it is far beyond any expectations we made when we planned the trial.

**PSB: How would these results compare with what you would expect with bicalutamide?**

**Prof Tombal:** In Europe, bicalutamide is registered and we still use it. If I take for instance, my personal patients, I would say 10-15% of the patients are treated with bicalutamide monotherapy.

**The problem with bicalutamide is that we know that the PSA drop is never what we see with LHRH agonists; we know it is a good drug, but the trial I have indicated, that it was a chemo-equivalent only for patient with minimal disease.**

Although we have no direct comparison, but we have historical comparison in Europe because we use bicalutamide a lot. If we just look at the PSA drop for instance [with en-

zalutamide], it is apparently much more profound than [we normally see] with bicalutamide. That is clear.

From the patients in the trial, we have observed objective tumor shrinkage, and sometimes very impressive one, something we have not seen very well with bicalutamide. We have no direct comparison, but it is clear from my perspective that it compares well with bicalutamide in terms of side effect profile because there is no castration syndrome, there is a little bit of gynecomastia, little bit of fatigue, things that are extremely well tolerated by the patient in comparison to LHRH agonists.

But the tumor response, seems – and I do insist – much better than with bicalutamide.

**PSB: So will you be planning any other head to head trials with bicalutamide or the LHRH agonists?**

**Prof Tombal:** The problem of drug development is that actually the leading dancers are the regulatory authorities. If you go to EMA, European Medicines Agency, because bicalutamide is accepted we could easily plan a trial head to head bicalutamide versus enzalutamide. The problem is that FDA never registered bicalutamide, so we have to see how they are going to behave. There are plans to conduct a trial, but the exact design of the trial, and we can't do nothing about this, will be decided by FDA. We don't even know right now whether it is going to be one global trial, or trial made for Europe and the US.

Interestingly also, in contrast to all the agents that have been developed in castration resistant prostate cancer, nobody has ever gone to FDA with a modern plan saying these are the problems, these are the compounds. We don't know how they will react.

Clearly if I had all the money and all the patients, the ideal trial would be a three arm trial comparing standard hormonal treatment to enzalutamide to bicalutamide. Because, if we do that then we could really have the answer both in term of survival and in term of quality of life.

I am a urologist by training, so most of the patients I see, I would say even 85%, they won't die from the disease. Those who have aggressive disease are seen mostly by medical oncologists. The medical oncologist concern is primarily to increase overall survival. Where my concern as a urologist is to get a similar overall survival, to keep the good result we have right now, but lower the toxicity. If I want to answer both questions at the same time, the ideal would be a three arm trial to get all the information on the quality of life and overall survival.

**PSB: I think the three arm trial would be most optimal and give the definitive answer**

**Prof Tombal:** That would be the more elegant and would be the one that would be the most scientifically satisfying.

**PSB: Are there any other combination trials with enzalutamide in that setting that have piqued your interest?**

**Prof Tombal:** If you give me \$1 million dollars and ask me what is the best combination, I would say it is enzalutamide and radium-223. Because, we know something in prostate

cancer, it is that there is something magical that is happening when you combine radiation therapy and hormonal treatment. That is where androgen deprivation therapy has been shown to increase overall survival. All the trials done by SWOG, EORTC and early work back in the 70's showing that if you hit the cell with some form of DNA breaking mechanism like radiotherapy plus hormone therapy you have got something magical.

To me, the association of a very effective anti-androgen and radiation therapy is something I want to see. One of the advantage on top of that is that these two drugs do not require corticoids and are extremely well tolerated. So this is really an association i don't fear. Radium-223 is well tolerated. In all these men we identify now with oligo-metastatic disease, combining these two drugs, give me the drug, give me the money, I would be extremely interested.

**PSB: Is that trial planned at all?**

**Prof Tombal:** I think both Bayer and Medivation are speaking to each other, so I am quite sure it is going to be planned sometime.

**Additional notes...**

Although I spoke to Prof Tombal prior to the meeting, I was quite unprepared for the sheer impressiveness of the waterfall plot, which showed a PSA response (i.e. a reduction > 80%) at 25 weeks of 92.5% with a fairly narrow CI (86.2-98.8%).

In a [previous interview](#), [Charles Sawyers](#), the co-inventor of enzalutamide discussed its potential development, including the translational opportunities beyond CRPC in earlier disease.

It looks likely, with these latest results, that enzalutamide has clear activity in advanced (hormonally-sensitive) prostate cancer and a three arm trial, as suggested by Prof Tombal, would actually answer the key question of which therapy would be the optimal solution in this setting. Hopefully, we will see more advances in this area emerge over the next couple of years. If successful, this would be a large potential market opportunity for enzalutamide, potentially much bigger than the CRPC setting before or after chemotherapy.

## Related Posts

- [Medivation announce interim results of PREVAIL in pre-chemotherapy CRPC](#)
- [Update on advanced prostate cancer including enzalutamide \(MDV3100\) and abiraterone](#)
- [Video Report from 2012 European Association of Urology Congress in Paris](#)
- [The challenge of prostate cancer drug approval versus reimbursement](#)
- [The role of the Androgen Receptor in breast cancer](#)
- [Is ARN-509 \(Aragon\) potentially better than MDV-3100 \(Medivation\) in advanced prostate cancer?](#)
- [Excellent news in Advanced Prostate Cancer - Medivation's MDV3100 meets primary endpoint](#)
- [Making a difference to the lives of cancer patients: An interview with Dr Charles Sawyers](#)

## Enzalutamide improves survival in chemo-naive metastatic prostate cancer

By: SUSAN LONDON, Oncology Practice Digital Network  
Jan. 28, 2014

### AT THE GENITOURINARY CANCERS SYMPOSIUM

Vitals

**Major finding:** Compared with placebo, enzalutamide yielded better overall survival (hazard ratio, 0.71) and radiographic progression-free survival (hazard ratio, 0.19).

**Data source:** An interim analysis of a randomized phase III trial in 1,717 men with chemotherapy-naive castration-resistant metastatic prostate cancer (PREVAIL trial)

**Disclosures:** Dr. Beer disclosed that he receives research funding from Cougar Biotechnology, Janssen Biotech, Astellas Pharma, and Medivation. The trial was sponsored by Medivation.

The androgen receptor-blocker enzalutamide is efficacious and safe in men with metastatic castration-resistant prostate cancer who have not received chemotherapy, according to interim results of the randomized phase III PREVAIL trial.

Patients who received enzalutamide (Xtandi) were 29% less likely to die and 81% less likely to experience radiographic progression than patients who received a placebo, researchers are reporting at the 2014 Genitourinary Cancers Symposium sponsored by the American Society of Clinical Oncology.

Enzalutamide also prolonged the median time to chemotherapy by 17 months and was associated with a nearly 12 times higher rate of response.

Safety results showed that the drug was well tolerated and not associated with an increase in the rate of treatment discontinuation because of adverse events.

"As a result of these observations, it is my view that enzalutamide provides a meaningful clinical benefit to men with metastatic prostate cancer," lead author Dr. Tomasz Beer, professor of medicine and deputy director of the Knight Cancer Institute at Oregon Health and Science University, Portland, commented in a press briefing before the symposium.



[Dr. Tomasz Beer]

The [PREVAIL](#) trial's findings would apply to roughly 50,000 men each year in the United States, he estimated. "For folks who develop metastatic prostate cancer, by and large, all of them at some point or another would be expected to have this metastatic hormone-resistant state that is represented in this study population."

The favorable interim results prompted the investigators to stop the trial early, in October 2013, and offer enzalutamide to patients in

the placebo arm. The manufacturer, [Medivation](#), plans to file with the Food and Drug Administration for a new indication for enzalutamide, which is currently approved for the treatment of castration-resistant metastatic prostate cancer in men who have received chemotherapy.

"This is a very important study from the perspective that this applies to patients who have not yet had chemotherapy, which may expand the regulatory approval of enzalutamide. And one key fact for me is that although chemotherapy is sort of held up as the benchmark for this disease, the reality is that our current data suggest that less than 50% of men with castration-resistant prostate cancer actually receive chemotherapy," noted press briefing moderator Dr. Charles J. Ryan, a professor at the University of California, San Francisco, and leader of the Genitourinary Medical Oncology Program.

"So this treatment should change the regulatory status of enzalutamide and would open up this possibility of therapy for a very large group of patients who currently have really only one or two treatment options available to them," Dr. Ryan commented.

Dr. Beer declined to directly compare the efficacy results of PREVAIL with those of [Cougar 302](#), a similar trial of the oral antiandrogen abiraterone (Zytiga) that led to its approval in this patient population.

But he noted that the trials' populations differed in some respects that may be important; for example, about 12% of patients in PREVAIL had visceral metastases, compared with none in Cougar 302. Also, the former study excluded patients with a history of seizure, whereas the latter excluded those with cardiac risk factors.

Should enzalutamide gain approval for this new indication, the choice between enzalutamide and abiraterone would likely be individualized, taking into account these factors as well as others such as the need to coadminister steroids and follow dietary restrictions with abiraterone, according to Dr. Beer.

"That's a decision that every clinician and patient will make in the clinic individually ... I don't think there is a blanket answer to that question for all patients," he said. "We have two active drugs, we are fortunate to have those, and my real hope is that the work we are currently doing on the research front as a part of the [\[Stand Up to Cancer\]](#) West Coast Dream Team and other such efforts will enable us to further define which patient populations benefit the most from which therapeutic approach and be able to answer this question in a scientific manner in the future."

The two drugs may be compared in a head-to-head trial and will likely be tested in sequence, in combination, and in earlier stages of the disease, he added.

In fact, Dr. Ryan, the press briefing moderator, pointed out that just last week, the U.S. cooperative group system [launched a trial](#) comparing the combination of enzalutamide and abiraterone with enzalutamide monotherapy.

PREVAIL was sponsored by Medivation and enrolled 1,717 men with metastatic prostate cancer who had experienced progression on androgen deprivation therapy but had not received chemotherapy. They had no or only mild symptoms.

The men were randomized evenly to double-blind treatment with enzalutamide (160 mg/day) or a placebo.

With a median follow-up of about 20 months, enzalutamide was associated with better overall survival (hazard ratio, 0.71; *P* less than .0001) and better radiographic progression-free survival (HR, 0.19; *P* less than .0001). In post hoc analyses, the findings were much the same in the small subset of patients who had visceral metastases, according to Dr. Beer.

The response rate was 59% with enzalutamide (20% complete response; 39% partial response), compared with just 5% with placebo (*P* less than .0001).

Enzalutamide also delayed the median time to receipt of chemotherapy – "a pragmatic measure of real-world treatment effect," he noted – from 11 to 28 months (HR, 0.35; *P* less than .0001).

The rate of grade 3 or worse adverse events was 43% with enzalutamide and 37% with placebo. The most common toxicities of any grade were fatigue, back pain, constipation, and arthralgia. The rate of treatment discontinuation from adverse events was identical at 6% in each arm.

Two patients (0.1%) – one in each study arm – experienced seizure, which has been a concern with enzalutamide; both were subsequently determined to have a history of seizure unknown to their enrolling physician, which would have excluded them from the trial.

"What that tells us is that with appropriate patient selection, this clinical trial demonstrates that the drug can be administered very safely from the perspective of seizure risk," Dr. Beer said. "In point of fact, in patients who didn't have a prior history of seizures, there were no seizures at all in this trial."

Dr. Beer disclosed that he receives research funding from Cougar Biotechnology, Janssen Biotech, Astellas Pharma, and Medivation. The trial was sponsored by Medivation.