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An Evaluation of the Effectiveness and Safety of Erleada®

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ABSTRACT

Prostate cancer is the fourth most common cancer worldwide; however, it remains a challenge for both patients and doctors alike to identify the proper treatment. Patients are hesitant to fully commit to medications and treatments due to the uncertainty surrounding the safety and effectiveness of products. Erleada®, or Apalutamide, is a newer drug that has shown promising results. Following intensive testing with the two clinical trials TITAN and SPARTAN, Erleada® is currently FDA approved for two kinds of prostate cancer, mCSPC and nmCRPC. Both trials ensured the effectiveness of Erleada® by contrasting results of patients using Erleada® against users of a placebo drug. Erleada® was shown to prolong metastasis-free survival for patients with nmCRPC, as well as lengthen radiographic progression-free survival for patients with mCSPC. The trials also established the safety of Erleada® through the low percentages of patients recorded to suffer from severe side effects of the drug. In addition, Erleada®'s efficacy was tested through a meta-analysis comparison of Erleada® with other similar non-chemotherapy oncology drugs, namely Nubeqa® and Xtandi®. Erleada® was proven to have the highest likelihood of being the most beneficial for the treatment of nmCRPC. This was measured through the metastasis-free survival and the prostate-specific antigen progression-free survival, both of which were lengthened by Erleada®. Overall, Erleada® is shown to have the potential to be a new miracle treatment for prostate cancer patients.

Introduction

According to the WHO (World Health Organization), cancer is a lethal and life-threatening disease, accounting for 1 in 6 deaths worldwide. As the second-leading cause of death, cancer is defined as the rapid growth of abnormal cells which overpower ordinary cells and prevent the body from properly functioning. To combat this risky illness, oncologists have spent years developing various treatment options, ranging from surgery to radiation to oncology drugs. Oncology drugs are easier to administer than other treatment options while still providing the desired result. These drugs can slow growth of cancer cells, prevent the spread of cancer to other body parts, shrink tumors, and even entirely eliminate cancer cells. However, there is a drawback: these drugs possess unwanted and sometimes fatal side effects. The problems these side effects pose differ amongst patients, as drugs can react differently person to person. With this uncertainty surrounding their safety, patients need to be wary of what they put into their body. Although this situation is evident regarding all oncology drugs, the spotlight will be laid on the use of a specific oncology drug, Erleada®. Erleada® is the brand name for Apalutamide, a hormone therapy medication for prostate cancer, the 4th most common cancer type with 1.41 million cases as of 2020. Prostate cancer is cancer that occurs in the prostate gland, located next to the bladder and rectum. The risk of prostate cancer increases with old age, family history of the cancer, obesity, and even race. Erleada® is a new drug in terms of distribution and usage, however its promising qualities have piqued the interest of many researchers. Although Erleada® has the ability to rehabilitate prostate cancer patients, Erleada® still has harmful side effects, including heart disease, strokes, fractures, seizures, and fertility problems. Less harmful but still detrimental side effects include tiredness, joint pain, rashes, decreased appetite, weight

loss, hypertension, hot flashes, and diarrhea. There is no clear-cut way to prevent side effects, however we can gauge the overall safety of a drug and weigh that against possible benefits to see if consuming the drug is worth it. Through an examination of prior clinical trials and a detailed comparison with other similar drugs, Erleada®'s effectiveness and safety will be evaluated.

About Erleada®

Before focusing on establishing Erleada®'s potency, it is essential to grasp the fundamentals of Erleada®. Erleada® is a life-changing medication for prostate cancer patients, possessing the ability to prolong survival and regulate the disease. Its magic revolves around its active substance, Apalutamide. Apalutamide was first referenced in a November 2007 patent application but was only sold under the name Erleada® in recent years following numerous tests and clinical studies. The drug Apalutamide works as an Androgen Receptor Inhibitor. The two main androgens present in males are testosterone and dihydrotestosterone. The focus on males comes from the fact that a large majority of prostate cancer patients are male, as males are the only sex who have prostates. While female prostate cancer is possible, it develops in a different area called the Skene's glands. Following male puberty, the sudden growth of these androgens substantially grows the prostate from its prepubertal size. In other words, testosterone essentially serves as fuel for prostate cancer. Erleada® is mostly prescribed alongside ADT, or androgen deprivation therapy, which references treatments aimed to lower testosterone and disrupt the production of the androgens. ADT can't help prostate cancer for long periods of time on its own since it only initially stays effective, and eventually castration-resistant cancer will develop in all men. This means that eventually the cancer eventually won't respond to testosterone lowering treatment like ADT. Apalutamide functions opposite of the male hormone testosterone and prevents the androgen from binding with its androgen receptor. Together with ADT, Erleada® slows the growth of the cancer before the condition worsens.

Androgens are a sex hormone, helping with puberty and reproduction in both males and females, making Apalutamide a form of hormone therapy. Hormone therapy is commended to be a safer alternative to other forms of cancer treatment, especially chemotherapy. Chemotherapy is used to treat prostate cancer, with its most popular contender being Docetaxel, sold under the brand name Taxotere®. Chemotherapy is known to have toxic side effects, being capable of destroying healthy cells throughout the body. Even worse, it is difficult to predict how much of a benefit patients can get from Chemotherapy, with many patients not obtaining desired results but still suffering from side effects. Non-chemotherapy oncology drugs such as Erleada® are healthier substitutes, with less severe and hazardous side effects.

There were approximately 1.5 million people diagnosed with prostate cancer in 2020, with it being the most frequent cancer amongst males. Erleada® counters just two types of these prostate cancers: nmCRPC and mCSPC.

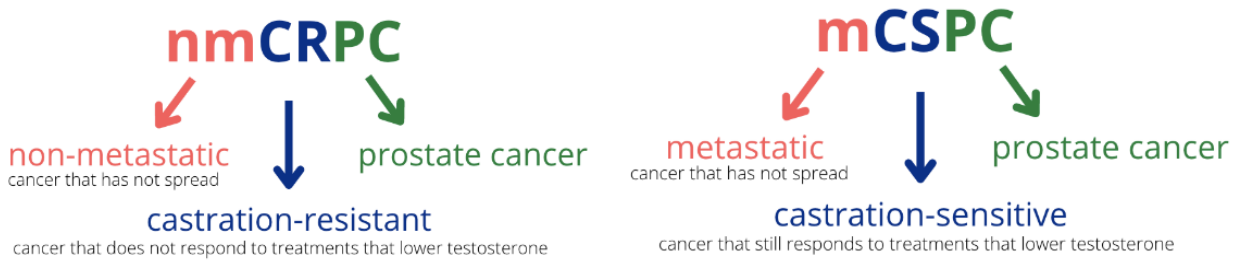

Figure 1. nmCRPC and mCSPC.

Although Erleada® is currently only used to combat these two types, it may be possible for the drug to be used for a more widespread array of prostate cancers in the near future. The drug is fairly newer in comparison to competitors, so it will take more years for the drug to undergo clinical trials and testing for other types of prostate

cancer. However, Erleada®'s encouraging results led to it being approved for usage just one year apart for both kinds of cancer.

Since then, the drug has been distributed through Janssen Pharmaceuticals, a verified company that overlooks all stages of the distribution process, from researching to prescription in pharmacy. Erleada® stands in a limited distribution network, where Janssen personally selects specialty pharmacy providers to distribute the medication. The drug is sold in a pill form, with the recommended dosage being 240 mg per day. Out of the patients treated with Erleada®, the median age was 68, as prostate cancer is more common amongst older men. The racial distribution for the drug stands at 68% caucasian, despite the fact that black people are shown to have a greater risk of prostate cancer and are more at risk for prostate cancer that is more aggressive. It was also researched that 92% of patients had a Gleanson score of 7 or higher. The Gleason score helps deduce which stage the cancer is; a score of 7 or higher translates into an intermediate to high grade cancer. This means the cells are more abnormal and are more likely to advance and spread. Erleada® can help patients with critical conditions such as these. So far, 50,000 patients plus have been prescribed Erleada®, successfully slowing down the growth of their cancer and lengthening their lives.

Clinical Trials

Erleada® can occasionally backfire and have severe side effects. These stem from the drug's potential to weaken bone and muscles as well as cause bleeding in the brain and obstruct heart arteries. Certain aspects of Erleada® are still uncharted territory, a prime example of this being the uncertainty around Erleada®'s effects on females and children, with oncologists being unsure if the drug is safe and functional for them. To ensure the drug's safety, Erleada® was studied in depth through two studies, TITAN and SPARTAN. The studies were funded by Janssen Research and Development, the pharmaceutical development company behind the acclaimed Johnson & Johnson corporation. TITAN established the use of Erleada® with mCSPC, while SPARTAN showed it was compatible with nmCRPC. Both were randomized clinical trials studying patients who orally took a 240 mg dose of Erleada® daily. The following are the results from the two trials.

TITAN trial

The TITAN trials consisted of a total of 525 patients receiving apalutamide and ADT (Androgen-deprivation therapy) and 527 receiving placebo and ADT, totaling 1052 test subjects. By utilizing ADT in the clinical trials, the researchers were able to replicate real life situations, as Erleada® is most often prescribed along with ADT. The main endpoints, or what the researchers measured throughout the investigation, were radiographic progression-free survival and overall survival. Radiographic progression-free survival is the time till the first time the progression of the disease is documented, or till death. Results showed that 68.2% of patients taking apalutamide were radiographic progression-free as of 24 months. In comparison, 47.5% patients with placebo were radiographic progression-free in the same time frame. This means that Erleada® was successful in keeping the cancer from progressing.

SPARTAN trial

The SPARTAN trial followed the results of 1207 patients with nmCRPC, 806 of which were on apalutamide and 401 of which were on placebo. By comparing the results of Erleada® vs a placebo, the researchers were able to calculate how the drug alters the results found in the experiment. The main end point of the clinical trial was the metastasis-free survival, which they defined as the time till metastasis is detected on imaging, or death. Research showed that for the apalutamide group, the median amount of metastasis-free survival was 40.5 months. On the other hand, the placebo group's time rounded out at 16.2 months. This drastic difference proved the drug's capability of reducing metastasis. Metastasis is important because metastasis is the main cause of death in regard to prostate cancer. Spreading to a

different body part means the prostate cancer can harm the other areas, most commonly the lymph nodes, lungs, and liver. Preventing this can drastically prolong the survival of patients. In addition, it was found that apalutamide overdid placebo in many other categories as well, with it performing significantly better than placebo in terms of progression-free survival and time to symptomatic progression.

Results

Both trials proved the efficacy of Erleada® compared to alternatives. In terms of side effects, the following table covers the data of percentages of total patients who got each side effect garnered from both trials.

Side Effects from Erleada®

	Ischemic cardiovascular Events	Cerebrovascular Events	Fractures and Falls	Hypothyroidism	Seizure
TITAN	4.4%	1.9%	9%	--	--
SPARTAN	3.7%	2.5%	12%	--	--
Both	--	--	--	8%	0.4%
Both Death	0.3%	0.2%	0.4%	--	--

[1]Dashes signify lack of data. Percentages are the percentage of patients with the listed condition.

Overall, while it is needed to be wary of potential risks associated with taking Erleada®, the low percentages of patients affected by the listed diseases did not raise caution from researchers. In the SPARTAN trial, Erleada® displayed promising results, being able to slow down the disease by an average of more than 24 months, which translates into a 72% decrease in risk of death. The TITAN trial had similar findings, showing that the time of survival without the cancer progressing was longer with Erleada®. Following these trials, Erleada® became approved by the FDA, the US Food and Drug Administration, for prescription, in 2018 for nmCRPC and 2019 for mCSPC. Approval by the FDA guaranteed that the drug could meet quality standards and was ready for public usage.

Competitors

Many companies have manufactured their own oncology drugs meant to combat prostate cancer over the years, so what makes Erleada® stand out? Comparing Erleada® with its two biggest competitors as of 2022, Xtandi® and Nubeqa®, the answer to that question is clear. On the surface, all three drugs function in the same way; they are androgen receptor inhibitors taken in pill form. Both drugs also share similar side effects to Erleada®, with common ones including seizure, heart disease due to artery blockage, blood pressure problems, decreased appetite, and fertility problems. However, the outcomes of each of these drugs are different.

Xtandi®

Xtandi® is the brand name for the drug Enzalutamide, with the chemical formula C21H16F4N4O2S. It is currently FDA approved for 3 kinds of prostate cancer: mCSPC, mCRPC, and nmCRPC. To get FDA approval, the drug must be deemed safe for usage. This usually occurs through intensive testing and trials, which can take long periods of time.

Therefore, the approvals of Xtandi® for each kind of prostate cancer were staggered, with approval for nmCRPC coming in during 2012, mCRPC during 2014, and mCSPC during 2019. In comparison with Erleada®, the approval for nmCRPC came 6 years earlier for Xtandi®. On the other hand, Erleada® was able to get approved for mCSPC a few months before Xtandi® was, with Xtandi® getting approved on December 16th, 2019, and Erleada® getting approved September 17th, 2019. However, Erleada® lacks one thing found in Xtandi®; unlike Xtandi®, Erleada® is currently not approved to treat mCRPC, which stands for metastatic castration resistant prostate cancer. This is prostate cancer that has spread and does not respond to treatment that lowers testosterone. This kind of prostate cancer usually has lower survival rates compared to others. Xtandi® is currently one of the only non-chemotherapy oncology drug options for patients with this disease, showing the accomplishment of this drug. Xtandi® is manufactured through a collaboration between brands Pfizer and Astellas, both healthcare companies. The production of the drug was originally agreed upon by the companies Medivation INC and Astellas, however in 2016 Pfizer acquired Medivation INC and has continued with the commercialization of the drug ever since.

Nubeqa®

The other drug in question is Darolutamide, which is sold under the brand name Nubeqa® and has the chemical formula C19H19CIN6O2. It is utilized against nmCRPC and was approved for usage in 2019, one year after Erleada® and 7 years after Xtandi®. Even more recently, it was approved for patients with mHSPC on August 5th, 2022. mHSPC is metastatic hormone-sensitive prostate cancer, where cancer has spread but can still be treated with hormone-therapy. Not much data has been found on the use of this drug for mHSPC because of its very recent approval. As a new contender in the treatment of prostate cancer, Nubeqa®'s total worldwide sales stood at less than $70 million per a single period. In the same period, Xtandi® had sales totaling $309 million. Erleada®'s superior status reflected on its total sales, with the drug garnering $344 million in the same period. Nubeqa® is commercialized through the Bayer and Orion Corporation, another collaboration made for the sake of prostate cancer treatment.

Meta Analysis Comparison

In a meta-analysis comparison of Apalutamide (Erleada®), Enzalutamide (Xtandi®) , and Darolutamide (Nubeqa®) for nmCRPC, it was deduced that Apalutamide had the highest likelihood to be the most beneficial as a treatment for patients. The data used to come to this conclusion is shown in the tables below:

Metastasis-free survival

Treatment	***P* score (fixed)**	***P* score (random)**
Apalutamide	0.8809	0.8809
Enzalutamide	0.7852	0.7852
Darolutamide	0.3339	0.3339

PSA progression-free survival

Treatment	*P* score (fixed)	*P* score (random)
Apalutamide	1.0000	1.0000
Enzalutamide	0.6667	0.6667
Darolutamide	0.3333	0.3333

Overall survival

Treatment	*P* score (fixed)	*P* score (random)
Apalutamide	0.6594	0.6594
Enzalutamide	0.6589	0.6589
Darolutamide	0.6024	0.6024

The researchers used the P score of each treatment option for ranking, describing the P score as "a frequentist analog to the surface under the cumulative ranking curves" (Mori et al., 2020). The investigation measured the following two metrics: MFS and PSA PFS. MFS stands for metastasis-free survival. Measuring this metric is essentially measuring how long a patient stays alive without the spread of their cancer. In the analysis, it was shown that Apalutamide had an improved MFS rate than the other two drugs, meaning patients were in metastasis-free survival for longer. The other metric is the PSA PFS, which stands for prostate-specific antigen progression-free survival. This is defined as the time to the first antigen failure, or death. Apalutamide was measured to provide the maximum benefits out of all three prostate cancer treatments in regard to PSA PFS, signifying that Apalutamide was able to extend this time the longest. In terms of overall survival, Apalutamide also ranked the highest, being able to regulate the disease for patients and prevent the disease from progressing. This research establishes the efficacy of Erleada® compared to similar options.

Conclusion

Prostate cancer is a serious disease, being both widespread and difficult to battle. Finding the best way to combat prostate cancer safely and effectively has been a lasting challenge for healthcare professionals. The analysis of research proves that Erleada® can be the solution. Although there are apparent side effects associated with the drug, doctors and researchers have placed countermeasures to prevent negative reactions. For instance, doctors often prescribe drugs to combat side effects along with the prescription of Erleada®. In addition, it is required for patients to inform their healthcare provider about pre-existing medical conditions and medications they are currently on to predict any drug reactions. Erleada® is proven to have low chances of causing severe health issues and is proved to be more efficient compared to other non-chemotherapy oncology drugs in its treatment of nmCRPC and mCSPC. Erleada® is a drug only in its beginning stages and has many more patients to treat in the near future.

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