# Comprehensive Insights into Prostate Cancer Clinical Trials:
## From Diagnosis to FDA Approvals

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# Introduction

**Prostate cancer is the second most common cancer among men in the United States.**

Prostate cancer primarily manifests in older men, with the median age at diagnosis being around 66 years. The disease can range from slow-growing tumors, which might not pose significant health risks, to aggressive forms that can spread quickly. The most common type is adenocarcinoma, which begins in the gland cells of the prostate. Other, less common types include small cell carcinoma, neuroendocrine tumors, and transitional cell carcinoma.

Prostate cancer remains one of the most prevalent cancers affecting men worldwide, with significant implications for public health. The development of effective treatments relies heavily on the successful execution of clinical trials. This whitepaper aims to provide a comprehensive overview of the critical aspects of prostate cancer clinical trials, addressing the multifaceted challenges and advancements in this field.

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# Evolution of Understanding

## Historical Perspectives

The understanding and management of prostate cancer has evolved significantly over the decades. The introduction of the prostate-specific antigen (PSA) test in the late 1980s marked a pivotal shift in early detection. Prior to this, most prostate cancers were diagnosed at an advanced stage due to a lack of effective screening tools. The PSA test enabled earlier diagnosis, leading to better outcomes for many men.

Treatment modalities have also seen substantial advancements. Initially, radical prostatectomy, an invasive surgical procedure, was the primary treatment for localized prostate cancer. Over time, less invasive techniques like laparoscopic and robotic-assisted surgeries have become more common, offering similar efficacy with reduced recovery times. Radiation therapy has also evolved, with the advent of more precise techniques like intensity-modulated radiation therapy (IMRT) and proton therapy, which minimize damage to surrounding tissues.

Research has continually pushed the boundaries of understanding, identifying genetic markers that predispose individuals to prostate cancer. The development of targeted therapies, such as androgen deprivation therapy (ADT) and newer androgen receptor inhibitors, has transformed the treatment landscape, especially for advanced or metastatic disease.

## Contributing Factors

### Biological Factors

- Age is the most significant risk factor, with the likelihood of developing prostate cancer increasing as men grow older. Family history also plays a crucial role; men with a father or brother who has had prostate cancer are at a higher risk. Genetic mutations, particularly in the BRCA1 and BRCA2 genes, have been linked to an increased risk of prostate cancer.

### Psychological Factors

- The psychological impact of a prostate cancer diagnosis can be profound, leading to anxiety, depression, and stress. Effective coping mechanisms and psychological support are essential components of comprehensive care.

### Environmental Factors

- Diet and lifestyle choices significantly impact prostate cancer risk. High-fat diets, particularly those rich in animal fats, have been associated with a higher risk. Conversely, diets high in fruits, vegetables, and fish may offer protective benefits. Exposure to certain chemicals and industrial hazards has also been implicated in increased prostate cancer risk.

# Prevalence, Trends, and Market Analysis

## Prevalence and Trends

Prostate cancer remains one of the most diagnosed cancers in men, with approximately 1 in 8 men expected to be diagnosed during their lifetime. According to the American Cancer Society (ACS), there will be about 299,010 new cases of prostate cancer and approximately 35,250 deaths from the disease in 2024, making it the second leading cause of cancer death in American men, behind only lung cancer.

The incidence rate of prostate cancer has exhibited notable changes over the past decade. Between 2007 and 2014, there was a significant decline in diagnosed cases, attributed to changes in screening recommendations that led to fewer men being screened. However, since 2014, the incidence rate has increased by about 3% per year overall and by approximately 5% per year for advanced-stage prostate cancer.

Despite these rising incidence rates, mortality rates for prostate cancer have declined. This decline is due to improvements in early detection and treatment, including the widespread use of PSA (prostate-specific antigen) testing and the development of more effective therapies. Consequently, survival rates have improved significantly. As of 2021, there were an estimated 3.4 million men living with prostate cancer in the United States.

## Market Analysis

The global market for prostate cancer treatment was valued at approximately $10 billion in 2023. The market is projected to grow at a compound annual growth rate (CAGR) of 5% over the next decade. Several factors contribute to this growth:

1. **Increasing Incidence:** The rise in prostate cancer cases, particularly in older populations, is driving demand for treatment options.
2. **Aging Population:** As the global population ages, the number of prostate cancer cases is expected to increase.
3. **Advancements in Treatment Modalities:** Innovations in surgery, therapies, and new drug developments are improving patient outcomes and increasing demand for these treatments.
4. **Expanding Healthcare Access:** Increased access to healthcare services in emerging markets is enabling more men to receive diagnosis and treatment, further expanding the market.
5. **Development and Approval of New Therapies:** Ongoing development and approval of new drugs and therapies are expected to provide better outcomes and improve the quality of life for patients, thereby driving market growth.

# Key Drugs for Prostate Cancer with Highest Earning Potential

Although there is some overlap with the most commonly prescribed FDA-approved drugs, focusing on earning potential provides insights into economic performance and strategic market positioning.

## 1. Xtandi (Enzalutamide)

- Xtandi, manufactured by Astellas/Pfizer, is an androgen receptor inhibitor extensively used for its proven efficacy in prolonging survival and improving the quality of life for patients with metastatic castration-resistant prostate cancer (mCRPC). It holds approximately 30% of the market share due to its widespread adoption and effectiveness. Future market projections for Xtandi are optimistic, driven by expanding indications and ongoing clinical trials. In 2023, Xtandi's estimated annual sales reached $4.2 billion, highlighting its strong market presence.

## 2. Zytiga (Abiraterone Acetate)

- Zytiga, produced by Janssen Biotech, is widely used for treating both metastatic castration-resistant and high-risk castration-sensitive prostate cancer. It commands approximately 25% of the market share, reflecting its effectiveness in significantly extending survival rates. The future market for Zytiga remains robust, supported by its established efficacy and potential for use in combination therapies with emerging treatments. In 2023, Zytiga achieved estimated annual sales of $3.5 billion.

## 3. Erleada (Apalutamide)

- Erleada, another key drug from Janssen Biotech, serves as an androgen receptor inhibitor used primarily for non-metastatic castration-resistant prostate cancer (CRPC). It is extensively used due to its effectiveness in delaying metastasis. Erleada holds approximately 15% of the market share due to its demonstrated benefits. In 2023, its estimated annual sales were $1.3 billion.

## 4. Lupron Depot (Leuprolide Acetate)

- Manufactured by AbbVie, Lupron Depot is a GnRH agonist extensively used to treat advanced prostate cancer. It maintains approximately 10% of the market share, supported by its reliability and patient adherence benefits. The future market for Lupron Depot is stable, with potential incremental growth. In 2023, its estimated annual sales were $1.2 billion.

## 5. Provenge (Sipuleucel-T)

- Provenge, developed by Dendreon, is an autologous cellular immunotherapy specifically used for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). It occupies approximately 5% of the market share due to its niche application and higher costs. Future market projections for Provenge are cautiously optimistic. In 2023, it generated $300 million in estimated annual sales.

# ICD-11 Code for Prostate Cancer

## ICD-11 Code for Prostate Cancer: 2C82

The ICD-11 criteria for diagnosing prostate cancer involves a combination of clinical presentation, imaging studies, and histopathological confirmation.

1. **Clinical Presentation:** Patients often present with symptoms including difficulty urinating, frequent urination, blood in urine or semen, erectile dysfunction, and pelvic discomfort or pain.
2. **Prostate-Specific Antigen (PSA) Testing:** Elevated levels of PSA in the blood can indicate prostate cancer, although elevated levels can also be seen in benign conditions.
3. **Digital Rectal Exam (DRE):** This physical examination allows physicians to feel the prostate gland for abnormalities such as lumps or hard areas.
4. **Imaging Studies:** Imaging techniques such as transrectal ultrasound (TRUS), magnetic resonance imaging (MRI), and computed tomography (CT) scans are used to visualize the prostate and surrounding tissues.
5. **Biopsy:** The definitive diagnosis of prostate cancer is made through a biopsy, where tissue samples from the prostate are examined under a microscope for cancerous cells.

## Evolution of Diagnostic Criteria

The diagnostic criteria for prostate cancer have evolved significantly over the years. Initially, the diagnosis was heavily reliant on clinical symptoms and physical examination findings. The introduction of PSA testing in the late 1980s revolutionized the early detection of prostate cancer, allowing for the identification of asymptomatic cases and leading to earlier and more effective treatment interventions.

### Impact of Changes on Clinical and Research Perspectives

- **Clinical Practice:** The refinement of diagnostic tools and criteria has led to earlier detection and treatment of prostate cancer, significantly improving patient outcomes.
- **Research Perspectives:** The advancements in diagnostic criteria have opened new avenues for research, particularly in the areas of biomarker discovery and personalized medicine. Researchers are increasingly focused on identifying genetic and molecular markers that can predict the aggressiveness of prostate cancer and the response to specific treatments. This has led to the development of targeted therapies and the potential for more individualized treatment.

# Epidemiology

## 1. Age

- The likelihood of developing prostate cancer increases markedly as men age. This is due to cellular changes, hormonal changes, and cumulative exposure to environmental factors and lifestyle choices that can contribute to cancer risk.
- According to the American Cancer Society, about 60% of prostate cancer cases are diagnosed in men aged 65 and older. This overwhelming prevalence in older age groups highlights age as the highest risk factor for prostate cancer.

## 2. Racial Group

- Racial and ethnic background play a crucial role in the incidence of prostate cancer. African American men have the highest incidence rates of prostate cancer in the United States and are more likely to be diagnosed at an advanced stage and have higher mortality rates compared to men of other racial groups. This disparity is due to a combination of genetic, environmental, and socioeconomic factors.

## 3. Geographic Location

- Geographic variations in prostate cancer incidence and mortality rates are evident worldwide. High incidence rates are reported in North America, Australia, and Western Europe, while Asian countries, including Japan and China, report lower rates. These variations can be attributed to genetic predisposition, lifestyle factors, dietary habits, and the availability of screening and diagnostic facilities.

## 4. Genetic Predisposition

- Genetics play a significant role in the risk of developing prostate cancer. Men with a family history of prostate cancer are at a higher risk. Having a father or brother with prostate cancer more than doubles a man's risk. This risk increases further if multiple family members are affected or if relatives were diagnosed at a younger age.
- Certain genetic mutations have been linked to an increased risk of prostate cancer. Mutations in the BRCA1 and BRCA2 genes, typically associated with breast and ovarian cancers, are also linked to a higher risk of prostate cancer. Men with Lynch syndrome, a hereditary condition that increases the risk of several cancers, also face an elevated risk.

## 5. Environmental Factors

- Environmental and lifestyle factors also significantly influence the epidemiology of prostate cancer. Diet, physical activity, and exposure to certain chemicals can affect the risk. Diets high in red meat and dairy products have been associated with increased risk, while those rich in fruits and vegetables may reduce the risk.
- Occupational exposure to certain chemicals, such as pesticides and industrial chemicals, has also been linked to an increased risk of prostate cancer. Additionally, obesity has been associated with a higher risk of aggressive prostate cancer, although the relationship between body weight and prostate cancer risk is complex and influenced by various factors

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# Pivotal Endpoints in Prostate Cancer Clinical Trials

**In the context of Prostate Cancer, understanding and identifying pivotal endpoints is crucial for the effective assessment of treatment outcomes in clinical trials and practice.**

### 1. Overall Survival (OS):

The time from the start of the treatment until death from any cause. Considered the gold standard for determining the efficacy of a cancer treatment. A significant improvement in OS is a strong indicator of the drug's effectiveness.

### 2. Progression-Free Survival (PFS):

The length of time during and after treatment that the patient lives with the disease without it worsening. Indicates the drug's ability to delay disease progression.

### 3. Metastasis-Free Survival (MFS):

The length of time that patients remain free from cancer spreading to distant organs. Particularly relevant for non-metastatic prostate cancer patients to prevent the progression to metastatic disease.

### 4. Time to Progression (TTP):

The time from the start of treatment until the disease starts to worsen. Measures the drug's effectiveness in delaying disease advancement.

### 5. Response Rate (RR):

The proportion of patients whose cancer shrinks or disappears after treatment. Reflects the drug's immediate effectiveness in reducing tumor size.

### 6. Quality of Life (QoL):

Measures patient-reported outcomes regarding their well-being and ability to perform daily activities. Ensures that the treatment does not significantly deteriorate the patient's quality of life despite clinical benefits.

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# Key Challenges in Determining Endpoints in Prostate Cancer Clinical Trials

## 1. Overall Survival (OS):

- OS requires **long-term follow-up**, which can be resource-intensive and time-consuming.
- **Large sample sizes** can be difficult to recruit and maintain.
- Patients may receive **subsequent treatments** after the trial therapy, which can confound results.

## 2. Progression-Free Survival (PFS):

- **Accurate and consistent measurement** of disease progression is essential.
- PFS is a **surrogate endpoint** and may not always correlate with overall survival or quality of life.
- **Frequent assessments** are required to detect progression, which can be burdensome for patients and increase trial costs.
- **Variability in disease biology** can result in different progression patterns, making it challenging to generalize findings.

## 3. Metastasis-Free Survival (MFS):

- Requires **extended follow-up** to detect metastasis, increasing the duration and cost of trials.
- The long follow-up period can lead to **higher dropout rates**, potentially biasing the results.
- Different imaging modalities and criteria for detection can introduce **variability** and affect reliability of MFS as an endpoint.

## 4. Time to Progression (TTP):

- **Clear and consistent criteria** for defining disease progression are necessary, but this can vary depending on the trial.
- **Requires frequent monitoring** and assessments to accurately capture the time to progression. This can be resource-intensive.
- TTP assessment can be **subjective**, leading to potential biases.
- **Subsequent treatments** after progression can confound the results and make it difficult to isolate effects of initial treatment.

## 5. Response Rate (RR):

- A **short-term measure** and may not reflect long-term benefits.
- **Variability in tumor biology** can result in different responses to treatment, complicating the interpretation of response rates.
- Requires **objective criteria** (e.g., RECIST) to measure tumor shrinkage, which can be challenging to apply consistently.
- **Differentiating between partial and complete responses** and understanding their implications can be complex.

## 6. Quality of Life (QoL):

- QoL assessments are **subjective** and can vary widely.
- **Requires comprehensive, validated tools** to accurately capture QoL, which can be time-consuming to administer and analyze.
- Ensuring **consistent and accurate patient reporting** over the course of the trial can be challenging.

# FDA-Approved Drugs for Prostate Cancer

## Hormonal (Androgen Deprivation Therapy, ADT)

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Leuprolide (Lupron) | 1985 | AbbVie | GnRH agonist | Lowers testosterone levels |
| Goserelin (Zoladex) | 1989 | AstraZeneca | GnRH agonist | Lowers testosterone levels |
| Triptorelin (Trelstar) | 2000 | Ipsen | GnRH agonist | Lowers testosterone levels |
| Degarelix (Firmagon) | 2008 | Ferring Pharmaceuticals | GnRH antagonist | Lowers testosterone levels |
| Abiraterone (Zytiga) | 2011 | Janssen Biotech | CYP17 inhibitor | Reduces androgen production |
| Enzalutamide (Xtandi) | 2012 | Astellas Pharma | Androgen receptor inhibitor | Blocks androgen receptor signaling |
| Apalutamide (Erleada) | 2018 | Janssen Biotech | Androgen receptor inhibitor | Blocks androgen receptor signaling |
| Bicalutamide (Casodex) | 1995 | AstraZeneca | Androgen receptor inhibitor | Blocks androgen receptor signaling |

## Chemotherapy

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Docetaxel (Taxotere) | 2004 | Sanofi | Microtubule inhibitor | Inhibits cell division |
| Cabazitaxel (Jevtana) | 2010 | Sanofi | Microtubule inhibitor | Inhibits cell division |

# FDA-Approved Drugs for Prostate Cancer (cont.)

## Radiopharmaceuticals

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Radium-223 (Xofigo) | 2013 | Bayer | Alpha particle-emitting radiopharmaceutical | Targets bone metastases |

## Bone-targeting Agents (to prevent or treat bone metastases)

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Denosumab (Xgeva) | 2010 | Amgen | RANKL inhibitor | Prevents bone resorption |
| Zoledronic acid (Zometa) | 2001 | Novartis | Bisphosphonate | Prevents bone resorption |

## Immunotherapy

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Sipuleucel-T (Provenge) | 2010 | Dendreon | Autologous cellular immunotherapy | Stimulates immune response against cancer cells |

## PARP Inhibitors (for patients with specific genetic mutations)

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Olaparib (Lynparza) | 2014 | AstraZeneca | PARP inhibitor | Inhibits DNA repair in cancer cells with BRCA mutations |
| Rucaparib (Rubraca) | 2016 | Clovis Oncology | PARP inhibitor | Inhibits DNA repair in cancer cells with BRCA mutations |

# Pivotal Clinical Trials Leading to FDA Approval

| Drug Name | Clinical Trial Identifier | Sample Size | Key Findings and Statistical Data |
|---|---|---|---|
| Abiraterone | NCT00638690 | 1195 | • Significant improvement in overall survival; median OS 34.7 months vs 30.3 months for placebo. |
| Enzalutamide | NCT01212991 | 1717 | • Extended survival; median OS 18.4 months vs 13.6 months for placebo. |
| Apalutamide | NCT01946204 | 1207 | • Delayed metastasis; median metastasis-free survival 40.5 months vs 16.2 months for placebo. |
| Docetaxel | TAX 327 Study | 1006 | • Docetaxel administered every three weeks demonstrated a significant survival benefit compared to Mitoxantrone. |
| Flutamide | NCT00002597 | 2028 | • Improved response rate: significant decrease in PSA levels compared to placebo. |
| Goserelin | GDCT0140377 | 352 participants | • Findings suggested that high-dose radiotherapy (HDRT) with long-term androgen deprivation (LTAD) was effective when compared to HDRT plus short-term androgen deprivation (STAD). |
| Bicalutamide | NCT00673205 | 8113 participants | • The study assessed the effect of Bicalutamide as adjuvant or immediate hormonal therapy versus placebo in patients' post-primary therapy or on watchful waiting, showing significant benefits in locally advanced prostate cancer. |

# Approved Product Analysis: Abiraterone

## COU-AA-301: Patients with metastatic CRPC who had received prior docetaxel chemotherapy

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients whom had received a GnRH or had prior bilateral orchiectomy | Primary Survival Analysis | ECOG, PSA, (BPI-sf) | Interim Analysis | ZYTIGA with Prednisone (N=797) | Median survival 14.8 months vs. 10.9 months; p<0.0001; HR=0.646 (95% CI: 0.543, 0.768) |
| Patients whom had received a GnRH or had prior bilateral orchiectomy | Primary Survival Analysis | ECOG, PSA, (BPI-sf) | Interim Analysis | Placebo with Prednisone (N=398) | Median survival 10.9 months (95% CI: 10.2, 12.0) |
| Patients whom had received a GnRH or had prior bilateral orchiectomy | Updated Survival Analysis | ECOG, PSA, (BPI-sf) | Final Analysis | ZYTIGA with Prednisone (N=797) | Median survival 15.8 months vs. 11.2 months; HR=0.740 (95% CI: 0.638, 0.859) |
| Patients whom had received a GnRH or had prior bilateral orchiectomy | Updated Survival Analysis | ECOG, PSA, (BPI-sf) | Final Analysis | Placebo with Prednisone (N=398) | Median survival 11.2 months (95% CI: 10.4, 13.1) |

# Approved Product Analysis: Abiraterone (cont.)

## COU-AA-302: Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with metastatic CRPC | Overall Survival | ECOG, (BPI-sf) | Final Analysis (conducted after 741 deaths) | ZYTIGA with Prednisone (N=546) | Median survival 34.7(95% CI: (32.7, 36.8) months vs. 30.3 months; p=0.0033; HR=0.81 (95% CI: 0.70, 0.93) |
| Patients with metastatic CRPC | Overall Survival | ECOG, (BPI-sf) | Final Analysis (conducted after 741 deaths) | Placebo with Prednisone (N=542) | Median survival 30.3 months (95% CI: 28.7, 33.3) |
| Patients with metastatic CRPC | Radiographic Progression-free Survival | ECOG, (Prostate Cancer Working Group 2 criteria), RECIST | Final Analysis (conducted after 741 deaths) | ZYTIGA with Prednisone (N=546) | Median rPFS NR (11.66 months, NR); p<0.0001; HR=0.425 (95% CI: 0.347, 0.522) |
| Patients with metastatic CRPC | Radiographic Progression-free Survival | ECOG, (Prostate Cancer Working Group 2 criteria), RECIST | Final Analysis (conducted after 741 deaths) | Placebo with Prednisone (N=542) | Median rPFS 8.28 months (95% CI: 8.12, 8.54) |

# Approved Product Analysis: Abiraterone (cont.)

## LATITUDE: Patients with metastatic high-risk CSPC

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with metastatic high-risk CSPC | Overall Survival | ECOG, (BPI-sf) | Interim Analysis (conducted after 406 deaths) | ZYTIGA with Prednisone (N=597) | Median survival NE vs. 34.7 months; p<0.0001; HR=0.62 (95% CI: 0.51, 0.76) |
| Patients with metastatic high-risk CSPC | Overall Survival | ECOG, (BPI-sf) | Interim Analysis (conducted after 406 deaths) | Placebo(N=602) | Median survival 34.7 months (95% CI: 33.1, NE) |
| Patients with metastatic high-risk CSPC | Updated Overall Survival | ECOG, (BPI-sf) | Final Analysis (conducted after 618 deaths) | ZYTIGA with Prednisone (N=597) | Median survival 53.3 months (95% CI:48.2, NE)vs. 36.5 months; HR=0.66 (95% CI: 0.56, 0.78) |
| Patients with metastatic high-risk CSPC | Updated Overall Survival | ECOG, (BPI-sf) | Final Analysis (conducted after 618 deaths) | Placebo(N=602) | Median survival 36.5 months (95% CI: 33.5, 40.0) |

# Approved Product Analysis: Enzalutamide

## Patients with metastatic castration-resistant prostate cancer

| Study Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with metastatic castration-resistant prostate cancer | Overall Survival | ECOG, BPI-SF | Interim Analysis | XTANDI (N=800) | Median survival 18.4 months (95% CI: 17.3, NR)vs. 13.6 months; p<0.0001; HR=0.63 (95% CI: 0.53, 0.75) |
| Patients with metastatic castration-resistant prostate cancer | Overall Survival | ECOG, BPI-SF | Interim Analysis | Placebo (N=399) | Median survival 13.6 months (95% CI: 11.3, 15.8) |

# Approved Product Analysis: Apalutamide

## TITAN (NCT02489318): Metastatic Castration-sensitive Prostate Cancer (mCSPC)

| Study Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with mCSPC | Overall Survival | ECOG | Interim Analysis | ERLEADA (N=525) | Median survival NE vs. NE; HR=0.67 (95% CI: 0.51, 0.89); p=0.0053 |
| Patients with mCSPC | Overall Survival | ECOG | Interim Analysis | Placebo (N=527) | Median survival NE (95% CI: NE, NE) |
| Patients with mCSPC | Overall Survival | ECOG | Final Analysis (405 deaths) | ERLEADA (N=525) | Median survival NE vs. 52 months; HR=0.65 (95% CI: 0.53, 0.79) |
| Patients with mCSPC | Overall Survival | ECOG | Final Analysis (405 deaths) | Placebo (N=527) | Median survival 52 months (95% CI: 42, NE) |
| Patients with mCSPC | Radiographic Progression-free Survival | ECOG, PCWG2, RECIST | Interim Analysis | ERLEADA (N=525) | Median rPFS NE vs. 22.1 months; HR=0.48 (95% CI: 0.39, 0.60); p<0.0001 |
| Patients with mCSPC | Radiographic Progression-free Survival | ECOG, PCWG2, RECIST | Interim Analysis | Placebo (N=527) | Median rPFS 22.1 months (95% CI: 18.3, 33) |

# Approved Product Analysis: Apalutamide (cont.)

## SPARTAN (NCT01946204): Non-metastatic, Castration-resistant Prostate Cancer (nmCRPC)

| Study Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with nmCRPC | Metastasis-Free Survival | BICR, PSA, PSADT, ECOG | Final Analysis | ERLEADA (N=806) | Median MFS 40.5 months vs. 16.2 months; HR=0.28 (95% CI: 0.23, 0.35); p<0.0001 |
| Patients with nmCRPC | Metastasis-Free Survival | BICR, PSA, PSADT, ECOG | Final Analysis | Placebo (N=401) | Median MFS 16.2 months (95% CI: 15, 18) |
| Patients with nmCRPC | Time to Metastasis (TTM) | BICR, PSA, PSADT, ECOG | Final Analysis | ERLEADA (N=806) | Median TTM 40.5 months vs. 16.6 months; HR=0.27 (95% CI: 0.22, 0.34); p<0.0001 |
| Patients with nmCRPC | Time to Metastasis (TTM) | BICR, PSA, PSADT, ECOG | Final Analysis | Placebo (N=401) | Median TTM 16.6 months (95% CI: 15, 18) |
| Patients with nmCRPC | Progression-Free Survival (PFS) | BICR, PSA, PSADT, ECOG | Final Analysis | ERLEADA (N=806) | Median PFS 40.5 months vs. 14.7 months; HR=0.29 (95% CI: 0.24, 0.36); p<0.0001 |
| Patients with nmCRPC | Progression-Free Survival (PFS) | BICR, PSA, PSADT, ECOG | Final Analysis | Placebo (N=401) | Median PFS 14.7 months (95% CI: 14, 18) |
| Patients with nmCRPC | Overall Survival (OS) | BICR, PSA, PSADT, ECOG | Final Analysis | ERLEADA (N=806) | Median OS 73.9 months vs. 59.9 months; HR=0.78 (95% CI: 0.64, 0.96); p=0.0161 |
| Patients with nmCRPC | Overall Survival (OS) | BICR, PSA, PSADT, ECOG | Final Analysis | Placebo (N=401) | Median OS 59.9 months (95% CI: 53, NE) |

# Approved Product Analysis: Docetaxel

## Hormone Refractory Prostate Cancer

| Study Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with Karnofsky Performance Status (KPS) ≥60 | Overall Survival | KPS | Final Analysis | Docetaxel + Prednisone every 3 weeks (N=335) | Median survival 18.9 months vs. 16.5 months; HR=0.761 (95% CI: 0.619, 0.936); p=0.0094 |
| Patients with Karnofsky Performance Status (KPS) ≥60 | Overall Survival | KPS | Final Analysis | Mitoxantrone + Prednisone every 3 weeks (N=337) | Median survival 16.5 months (95% CI: 14.4-18.6) |
| Patients with Karnofsky Performance Status (KPS) ≥60 | Overall Survival | KPS | Final Analysis | Docetaxel + Prednisone weekly (N=334) | No significant overall survival advantage compared to Mitoxantrone |

# Approved Product Analysis: Flutamide

## CASODEX 50 mg Daily in Combination with an LHRH-A

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with previously untreated advanced prostate cancer | Overall Survival | KPS, PSA, QoL Questionnaire | Median follow-up of 160 weeks | Casodex + LHRH-A (N=404) | Hazard ratio for time to death: 0.87 (95% CI: 0.72 to 1.05) |
| Patients with previously untreated advanced prostate cancer | Overall Survival | KPS, PSA, QoL Questionnaire | Median follow-up of 160 weeks | Flutamide + LHRH-A (N=409) | 213 deaths in Casodex group, 235 deaths in Flutamide group |
| Patients with previously untreated advanced prostate cancer | Time to Progression | KPS, PSA, QoL Questionnaire | Median follow-up of 160 weeks | Casodex + LHRH-A (N=404) | Hazard ratio for time to progression: 0.93 (95% CI: 0.79 to 1.10) |
| Patients with previously untreated advanced prostate cancer | Time to Progression | KPS, PSA, QoL Questionnaire | Median follow-up of 160 weeks | Flutamide + LHRH-A (N=409) | No significant difference in time to objective tumor progression |

# Approved Product Analysis: Flutamide (cont.)

**Safety Data from Clinical Studies using CASODEX 150 m; CASODEX 150 mg is not approved for use either alone or with other treatments**

| Study Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| CASODEX vs. Castration in M1 Group | Overall Survival | KPS, PSA | Interim Analysis | CASODEX 150 mg (N not specified) | Risk of death 25% higher; HR 1.25 (95% CI: 0.87 to 1.81) |
| CASODEX vs. Castration in M1 Group | Overall Survival | KPS, PSA | Interim Analysis | Castration (N not specified) | Risk of death 31% higher; HR 1.31 (95% CI: 0.97 to 1.77) |
| CASODEX vs. Castration in Locally Advanced Group | Overall Survival | KPS, PSA | Study Completion | CASODEX 150 mg (N=352) | Risk of death 25% higher; HR 1.25 (95% CI: 0.92 to 1.71) |
| CASODEX vs. Castration in Locally Advanced Group | Overall Survival | KPS, PSA | Study Completion | CASODEX 150 mg (N=140) | Risk of death 36% lower; HR 0.64 (95% CI: 0.39 to 1.03) |
| CASODEX vs. Placebo in Localized Watchful Waiting Group | Overall Survival | KPS, PSA | Median follow up 7.4 years | CASODEX 150 mg (N=1627) | 294 deaths (37.7%) in CASODEX group vs. 279 deaths (32.9%) in placebo group |
| CASODEX vs. Placebo in Localized Watchful Waiting Group | Overall Survival | KPS, PSA | Median follow up 7.4 years | Placebo (N=1627) | HR 1.16 (95% CI 0.99 to 1.37) |

# Approved Product Analysis: Goserelin

## Stage B2-C Prostatic Carcinoma

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with bulky primary prostate tumors (stage B2 or C) | Local failure rate | Not specified | 4 years | N=466 (231 ZOLADEX + flutamide + radiation, 235 radiation alone) | 16% vs 33% (P<0.001) |
| Patients with bulky primary prostate tumors (stage B2 or C) | Incidence of distant metastases | Not specified | 4 years | N=466 (231 ZOLADEX + flutamide + radiation, 235 radiation alone) | 27% vs 36% (P=0.058) |
| Patients with bulky primary prostate tumors (stage B2 or C) | Median disease-free survival | Not specified | Refer to magnitude of improvement | N=466 (231 ZOLADEX + flutamide + radiation, 235 radiation alone) | 4.4 years vs 2.6 years (P<0.001) |
| Patients with bulky primary prostate tumors (stage B2 or C) | Median disease-free survival with normal PSA level | Not specified | Refer to magnitude of improvement | N=466 (231 ZOLADEX + flutamide + radiation, 235 radiation alone) | 2.7 years vs 1.5 years (P<0.001) |

## Prostatic Carcinoma

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with advanced prostatic cancer | Long-term endocrine responses | Not specified | Not specified | Not specified | Similar between ZOLADEX and orchiectomy |
| Patients with advanced prostatic cancer | Objective responses | Not specified | Not specified | Not specified | Similar between ZOLADEX and orchiectomy |
| Patients with advanced prostatic cancer | Duration of survival | Not specified | Not specified | Not specified | Similar between ZOLADEX and orchiectomy in a comparative trial |

# Approved Product Analysis: Bicalutamide

## CASODEX 50 mg Daily in Combination with an LHRH-A

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with advanced prostate cancer | Survival rate | Kaplan-Meier probability | Median follow-up 160 weeks | N=813 (404 CASODEX + LHRH analog, 409 flutamide + LHRH analog) | No significant difference (HR=0.87, 95% CI 0.72-1.05) |
| Patients with advanced prostate cancer | Time to objective tumor progression | Kaplan-Meier curve | Median follow-up 160 weeks | N=813 (404 CASODEX + LHRH analog, 409 flutamide + LHRH analog) | No significant difference (HR=0.93, 95% CI 0.79-1.10) |
| Patients with advanced prostate cancer ** In the analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with CASODEX-LHRH analog therapy and 235 (57.5%) patients treated with flutamide-LHRH analog therapy had died.* | Quality of life | Self-administered questionnaires on: Pain; Social functioning; Emotional well-being; Vitality; Activity limitations; Bed disability; Overall health; Physical capacity; General symptoms; Treatment symptoms | Median follow-up 160 weeks | N=813 (404 CASODEX + LHRH analog, 409 flutamide + LHRH analog) | No consistent significant differences |

**Safety Data from Clinical Studies using CASODEX 150 mg CASODEX 150 mg is not approved for use either alone or with other treatments.**

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Patients with metastatic (M1) prostate cancer | Survival rate | Not specified | Interim analysis | N=Not specified | 25% higher risk of death (HR 1.25, 95% CI 0.87-1.81); 31% higher risk of death (HR 1.31, 95% CI 0.97-1.77) in CASODEX group vs. castration ** Data Safety Monitoring Board recommended that CASODEX treatment be discontinued* |
| Patients with locally advanced (T3-4, NX, M0) prostate cancer | Survival rate | Not specified | Study completion following discontinuation of all M1 patients | N=352 (larger trial), N=140 (smaller trial) | Larger trial: 25% higher risk of death in CASODEX group (HR 1.25, 95% CI 0.92-1.71); Smaller trial: 36% lower risk of death in CASODEX –group (HR 0.64, 95% CI 0.39-1.03) in the smaller trial |
| Patients with localized prostate cancer under watchful waiting | Death or time to disease progression | Not specified | Median follow-up 7.4 years | N=1627 (subset of 3 trials, N=8113) | Trend toward decreased survival in CASODEX arm (HR 1.16, 95% CI 0.99-1.37); 294 (37.7%) deaths in CASODEX group vs. 279 (32.9%) deaths in placebo group |

# Summary of Failed Drug Candidates for Prostate Cancer

| Name of Drug | Clinical Trial Identifier | Reason for Termination / Drug Failure |
|---|---|---|
| Enzalutamide | NCT01995513 | XTANDI (enzalutamide) in combination with abiraterone acetate and prednisone is safe but fails to show improvement in progression free survival when compared to abiraterone acetate and prednisone alone in treatment of subjects with metastatic castration-resistant prostate cancer (CRPC). |
| Abiraterone acetate | GDCT0265061 | Concomitant use of statins next to abiraterone acetate treatment did not demonstrate any enhancement of survival outcomes or clinical benefit in men with metastatic castration resistant prostate cancer. |
| Docetaxel | NCT00917748 | Based on the results of this trial, there were no statistically significant differences found between treatments in the quality-of-life measurements, physical activity level, functional status or the number or chemotherapy cycles tolerated. |
| Flutamide | NCT00006214 | Flutamide was not effective in preventing prostate cancer in subjects who have neoplasia of the prostate. |
| Apalutamide | NCT03412396 | Strategy of a pre-operative anti-androgen (non-castrating) neoadjuvant therapy prior to radical prostatectomy did not achieve the primary endpoint of reducing the expected frequency of adverse pathology. |

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# Common Failure Points in Clinical Trials for Prostate Cancer

### 1. Biomarker Variability:

PSA levels can fluctuate due to non-cancerous conditions, leading to potential misclassification of disease status.

**Solution:** Incorporating additional biomarkers and imaging techniques (e.g., multiparametric MRI) can improve diagnostic accuracy and help in distinguishing between benign conditions and cancer progression.

### 2. Resistance Mechanisms:

Treatment resistance leads to disease progression despite initial responses to therapy.

**Solution:** Research into combination therapies and the development of new agents targeting resistance pathways is essential. Trials should include adaptive designs to adjust treatment protocols based on emerging resistance patterns.

### 3. Tumor Heterogeneity:

Heterogeneity can result in variable responses to treatment and difficulty in identifying universally effective therapies.

**Solution:** Personalized medicine approaches, such as genetic and molecular profiling of tumors, can help tailor treatments to individual patients' tumor characteristics.

### 4. Small Sample Sizes:

Small sample sizes can lead to inconclusive or misleading results.

**Solution:** Increasing the sample size and conducting multi-center trials can enhance the robustness of findings. Using more rigorous statistical methods can also improve the reliability of the results.

### 5. Short Follow-Up Periods:

Short follow-up periods can miss long-term effects and outcomes.

**Solution:** Designing trials with longer follow-up periods and using surrogate endpoints that correlate with long-term outcomes can provide a more comprehensive evaluation of treatment efficacy.

### 6. Bias in Patient Selection:

Selection bias can lead to overestimation of treatment benefits and underestimation of risks.

**Solution:** Ensuring diverse and representative patient populations in trials can improve the external validity of the results. Randomized controlled trials with strict inclusion and exclusion criteria can help mitigate selection bias.

# Safety Concerns and Standard of Care Treatment Options

## Key Safety Concerns

1. **Hormone Therapy:**
   - **Cardiovascular Risks:** Hormone therapy is associated with an increased risk of cardiovascular events.
   - **Metabolic Changes:** ADT can lead to metabolic syndrome, characterized by weight gain, insulin resistance, and dyslipidemia, increasing the risk of diabetes and cardiovascular diseases.
   - **Bone Health:** Long-term use of ADT can cause bone thinning and increase the risk of fractures.
2. **Chemotherapy:**
   - **Myelosuppression:** A significant concern with chemotherapy is myelosuppression, leading to decreased production of blood cells. This condition increases the risk of infections, anemia, and bleeding.
   - **Gastrointestinal Toxicity:** Chemotherapy can cause nausea, vomiting, diarrhea, and mucositis.
   - **Peripheral Neuropathy:** Long-term use of chemotherapeutic agents can cause nerve damage.
3. **Radiation Therapy:**
   - **Bowel and Bladder Complications:** Radiation can cause proctitis, cystitis, and urinary incontinence.
   - **Secondary Cancers:** There is a small risk of developing secondary cancers in the irradiated field, necessitating long-term follow-up.

## Standard of Care Treatment Options

1. **Active Surveillance:**
   - For low-risk, localized prostate cancer, active surveillance is often recommended, which involves regular monitoring of PSA levels, digital rectal exams, and biopsies to track disease progression.
2. **Surgery:**
   - Radical prostatectomy, the surgical removal of the prostate gland, is a common treatment for localized prostate cancer.
3. **Radiation Therapy:**
   - Radiation therapy includes external beam radiation therapy (EBRT) and brachytherapy (internal radiation).
4. **Hormone Therapy:**
   - ADT is used in various stages of prostate cancer, including metastatic and recurrent diseases.
5. **Chemotherapy:**
   - Used primarily for metastatic castration-resistant prostate cancer (mCRPC), chemotherapy can improve survival.
6. **Targeted Therapies:**
   - Recent advancements have introduced targeted therapies for specific genetic mutations or advanced disease stages.

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# Enhancing Clinical Trial Protocols for Prostate Cancer

Improving the protocols for prostate cancer clinical trials is crucial to enhance the chances of FDA approval and improve patient outcomes. This involves addressing regulatory insights, optimizing trial design, ensuring patient safety, and incorporating innovative approaches.

## 1. Regulatory Insights:

- **Compliance with FDA Guidelines**
  - Ensuring that trial designs meet FDA requirements is essential. This includes adhering to Good Clinical Practice (GCP) standards and submitting detailed protocols for FDA review and approval.
- **Early and Continuous Communication with the FDA**
  - Engaging with the FDA early in the trial design process and maintaining ongoing communication can help identify and address potential issues proactively. This includes pre-IND meetings, and end-of-phase 2 meetings.

## 2. Optimizing Trial Design:

- **Adaptive Trial Designs**
  - This allows for modifications based on interim results without compromising the integrity of the study.
- **Stratification and Biomarker Integration**
  - Stratifying patients based on genetic and molecular markers can enhance the understanding of treatment effects in different subgroups.
- **Multicenter and International Trials**
  - Increasing the diversity of the patient population enhances the generalizability of the results and facilitates faster recruitment.

## 2. Ensuring Patient Safety:

- **Comprehensive Safety Monitoring**
  - Implementing detailed safety monitoring plans, including regular health assessments and adverse event reporting, ensures timely detection and management of potential risks.
- **Informed Consent Process**
  - Providing clear and thorough information to participants about the potential risks and benefits of the trial is crucial. The informed consent process should be ongoing, with updates provided as new information becomes available.

## 4. Incorporating Innovative Approaches:

- **Real-World Evidence and Digital Health Technologies**
  - Leveraging real-world evidence and digital health technologies can provide valuable insights into treatment effectiveness and patient experiences. These technologies can also facilitate remote monitoring and data collection.
- **Patient-Centered Endpoints**
  - Including patient-centered endpoints, such as quality of life and patient-reported outcomes, ensures that the trial measures outcomes that are meaningful to patients.

# Notable Key Opinion Leaders in Prostate Cancer Research

| Name | Specialty | Designation | Location | Brief Bio |
|---|---|---|---|---|
| Dr. Francis X Parnis (MBBS, FRACP) | Medical Oncology | Co-Founder, Adelaide Cancer Centre | South Australia | Dr. Francis X. Parnis is a highly experienced Medical Oncologist at the Icon Cancer Centre Adelaide. He co-founded the Adelaide Cancer Centre in March 1995, which has since grown into the largest private oncology facility in South Australia. Dr. Parnis specializes in a variety of malignancies, including prostate cancer, gastrointestinal cancers, genitourinary cancers, breast cancer, lung cancers, and mesothelioma. |
| Prof. Declan G Murphy (MBBS, FRACS, FRCS (Urol)) | Urology; Surgery; Oncology | Professor, Peter MacCallum Cancer Centre | Victoria, Australia | Professor Declan G. Murphy is the Director of Genitourinary (GU) Oncology and the Director of Robotic Surgery at the Peter MacCallum Cancer Centre. He is also a Professorial Fellow at the University of Melbourne. He has been recognized as Australia's top researcher in Urology by The Australian in 2020 and 2022, based on his extensive publications and citations. He is an internationally recognized expert in prostate cancer, a member of the Advanced Prostate Cancer Consensus Conference, and the Association of Academic European Urologists. |
| Dr. Aneta Suder (MBBS, FRACP) | Medical Oncology; Gynecologic Oncology | Medical Oncologist, Royal Brisbane and Women's Hospital | Queensland, Australia | Dr. Aneta Suder is a Medical Oncologist at the Royal Brisbane and Women's Hospital (RBWH) in Brisbane, Australia. She specializes in the treatment of gynecological cancers, genitourinary cancers (including prostate, bladder, and germ cell tumors), and breast cancer. Dr. Suder completed her medical degree (MBBS) at the University of Otago in New Zealand in 2001 and received her Fellowship of the Royal Australasian College of Physicians in Australia in 2011. |
| Assoc. Prof. Daniel Moon (MBBS, FRACS) | Urology; Oncology | Uro-Oncologist, Peter MacCallum Cancer Centre | Victoria, Australia | Associate Professor Daniel Moon is a leading urologist and expert in robotic surgery at the Peter MacCallum Cancer Centre in Melbourne, Australia. He specializes in robotic prostate and kidney surgeries and holds the highest volume of robotic surgeries in Victoria, having completed over 2000 major procedures. His contributions to the field include pioneering robotic partial nephrectomy in Australia and publishing the first Australian series on laparoscopic radical prostatectomy. |
| Dr. Justin S Peters (MBBS, FRACS) | Urology; Oncology | Senior Consultant Urologist, The Royal Melbourne Hospital | Victoria, Australia | Dr. Justin S. Peters is a senior Consultant Urologist at the Royal Melbourne Hospital. He has been practicing since 1985 and holds a private practice at Epworth Hospital. Dr. Peters has a particular interest in prostate cancer and urinary stone disease, and he began performing robotic radical prostatectomies in 2003 after training at the University of California, Irvine. His contributions to the field also include extensive work in the treatment of urological malignancies and general urology. |
| Dr. Louise Kostos (MBBS, FRACP) | Medical Oncology | Medical Oncologist, Peter MacCallum Cancer Centre | Victoria, Australia | Dr. Louise Kostos is a Consultant Medical Oncologist at the Peter MacCallum Cancer Centre in Melbourne, Australia. She has a particular interest in prostate cancer management. She is currently pursuing her PhD at Peter Mac, focusing on optimizing outcomes for men with metastatic castration-resistant prostate cancer receiving PSMA-targeted radioligand therapy. |

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

**Dr Sud Agarwal**
**Chief Executive Officer**
*BSc (Hons), MB ChB FANZCA DDU*
dr.sudhanshu@ingenucro.com

**Adam Moodie**
**Director, Scientific Engagement**
*BSc*
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com