Clinical Trial Protocol

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Study Title

Comparative Effectiveness of Apalutamide versus Enzalutamide in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): A Real-World Evidence Analysis

Background & Rationale

In mHSPC, recent advancements in androgen receptor inhibitors like apalutamide and enzalutamide have improved patient outcomes. Comparative effectiveness in real-world settings is crucial to understanding the differential impact of these treatments on patient populations beyond controlled clinical trials. This study aims to leverage secondary RWE sources to assess the effectiveness of apalutamide and enzalutamide.

Study Objectives
• To compare overall survival and progression-free survival in mHSPC patients treated with apalutamide versus enzalutamide.
• To assess quality-of-life outcomes and adverse event profiles between the two treatments in real-world settings.

Study Design

Observational, retrospective comparative effectiveness study using secondary RWE sources.

Data Sources

Data will be sourced from databases such as Flatiron Health, SEER-Medicare, or other electronic health records (EHRs) and claims databases.

Key Inclusion Criteria
• Population: Adult males diagnosed with mHSPC.
• Interventions: Treatment with apalutamide or enzalutamide.
• Outcomes: Overall survival, progression-free survival, quality of life, and adverse events.

Data Extraction & Analysis

Patient characteristics, treatment regimens, and outcomes will be extracted and compared between cohorts. Propensity score matching or inverse probability of treatment weighting (IPTW) will adjust for confounding factors.

Expected Outcomes
• Insights into the relative effectiveness of apalutamide vs. enzalutamide in real-world populations.
• Evidence on differential safety profiles to inform clinical decision-making.

Timeline

Estimated completion within 8 months, from data extraction to final analysis.

Background & Rationale

Metastatic hormone-sensitive prostate cancer (mHSPC) represents a clinical stage of prostate cancer where the disease has spread beyond the prostate gland and still responds to androgen deprivation therapy (ADT). The management of mHSPC has evolved significantly with the introduction of novel androgen receptor inhibitors, which have demonstrated an ability to improve patient outcomes when used in combination with ADT.

Apalutamide and enzalutamide are two such nonsteroidal antiandrogens that have been approved for the treatment of mHSPC. Both drugs bind to the androgen receptor and inhibit its action, thereby impeding the growth and proliferation of prostate cancer cells. While randomized controlled trials (RCTs) have provided evidence of the efficacy and safety of these agents, there is a growing need to understand how these treatments perform in a real-world setting, where patient populations are more heterogeneous and treatment regimens may vary.

Real-world evidence (RWE) is increasingly recognized as a valuable complement to RCTs, as it reflects the utilization and outcomes of treatments under routine clinical practice conditions. Secondary RWE sources, such as electronic health records (EHRs) and claims databases, offer a wealth of data that can be analyzed to gain insights into the effectiveness and safety of medical interventions in broader patient populations.

The comparative effectiveness of apalutamide versus enzalutamide in the real-world management of mHSPC has not been extensively studied. This gap in knowledge presents an opportunity to assess the differential impact of these treatments on outcomes such as overall survival, progression-free survival, quality of life, and adverse events. Understanding these differences is crucial for clinicians to make informed treatment decisions and for patients to receive the most appropriate care based on evidence that extends beyond the controlled environment of clinical trials.

Given the importance of these outcomes in the management of mHSPC and the potential for RWE to inform clinical practice, this study aims to leverage secondary RWE sources to compare the effectiveness of apalutamide and enzalutamide in a real-world setting. The findings from this analysis are expected to provide valuable insights that could influence treatment strategies and improve patient care in mHSPC.

Objectives

Primary Objectives

Overall Survival Comparison: To compare the overall survival (OS) of metastatic hormone-sensitive prostate cancer (mHSPC) patients treated with apalutamide versus those treated with enzalutamide in a real-world setting.

2. Progression-Free Survival Comparison: To compare the progression-free survival (PFS) of mHSPC patients treated with apalutamide versus those treated with enzalutamide in a real-world setting.

Secondary Objectives

Quality-of-Life Outcomes: To assess and compare the quality-of-life (QoL) outcomes for mHSPC patients treated with apalutamide versus enzalutamide in a real-world setting.

Adverse Event Profiles: To evaluate and compare the adverse event (AE) profiles of mHSPC patients treated with apalutamide versus enzalutamide, focusing on the incidence, severity, and types of AEs encountered in a real-world setting.

Exploratory Objectives

Subgroup Analyses: To perform subgroup analyses to explore the effectiveness and safety of apalutamide and enzalutamide across various patient demographics and clinical characteristics.

Treatment Patterns: To examine the real-world treatment patterns, including treatment duration and dose modifications, for apalutamide versus enzalutamide in the management of mHSPC.

Healthcare Utilization: To assess healthcare resource utilization associated with the treatment of mHSPC with apalutamide versus enzalutamide, including hospitalizations, emergency visits, and other relevant healthcare services.

Study Endpoints

Primary Endpoints

Overall Survival (OS): Time from initiation of treatment with apalutamide or enzalutamide to death from any cause.

2. Progression-Free Survival (PFS): Time from initiation of treatment with apalutamide or enzalutamide to disease progression or death from any cause, whichever occurs first.

Secondary Endpoints

Quality-of-Life Measures: Assessment of QoL using validated instruments specific to prostate cancer and general health status.

2. Adverse Events (AEs): Incidence and severity of AEs, classified according to the Common Terminology Criteria for Adverse Events (CTCAE).

Exploratory Endpoints

Subgroup Treatment Effectiveness: Effectiveness of apalutamide versus enzalutamide in predefined patient subgroups (e.g., age, comorbidities, prior treatments).

2. Treatment Patterns: Description of treatment modifications, including dose interruptions, reductions, and treatment discontinuations.

Healthcare Resource Utilization: Analysis of healthcare services used during treatment with apalutamide or enzalutamide, including inpatient and outpatient services, and associated costs.

Study Design

Overview

This study is an observational, retrospective comparative effectiveness study designed to evaluate the real-world effectiveness of apalutamide versus enzalutamide in the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). The study will utilize secondary real-world evidence (RWE) sources to compare overall survival (OS), progression-free survival (PFS), quality of life (QoL), and adverse event (AE) profiles between the two treatments.

Data Sources

Data for this study will be extracted from comprehensive databases such as Flatiron Health, SEER-Medicare, and other electronic health records (EHRs) and claims databases that contain information on patient demographics, treatment regimens, clinical outcomes, and healthcare utilization.

Study Population

The study will include adult male patients diagnosed with mHSPC who have been treated with either apalutamide or enzalutamide. The inclusion criteria are designed to reflect a broad spectrum of real-world patients, thus ensuring the generalizability of the study findings.

Interventions

The interventions of interest in this study are the treatments with apalutamide and enzalutamide. These treatments will be compared in terms of their effectiveness and safety profiles.

Outcomes

The primary outcomes of interest are overall survival and progression-free survival. Secondary outcomes include quality of life measures and adverse events. These outcomes will be assessed to determine the comparative effectiveness and safety of the two treatments in a real-world setting.

Data Extraction & Analysis

Data extraction will involve the collection of patient characteristics, treatment details, and outcome data. Comparative analyses will be conducted between the apalutamide and enzalutamide cohorts. To account for potential confounding factors, statistical methods such as propensity score matching or inverse probability of treatment weighting (IPTW) will be employed.

Expected Outcomes

The study is expected to provide insights into the relative effectiveness of apalutamide versus enzalutamide in real-world populations, as well as evidence on the differential safety profiles of these treatments. These findings will be valuable for informing clinical decision-making and may impact treatment guidelines for mHSPC.

Timeline

The study is anticipated to be completed within 8 months, encompassing all phases from data extraction to final analysis. This timeline allows for a thorough investigation of the comparative effectiveness of the treatments while ensuring timely dissemination of results.

Population

Study Population

The study population will consist of adult male patients who have been diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). The population will be identified from secondary real-world evidence (RWE) sources, including electronic health records (EHRs) and claims databases.

Inclusion Criteria

To be included in the study, participants must meet the following criteria:
• Diagnosis: Confirmed diagnosis of mHSPC.
• Treatment: Received treatment with either apalutamide or enzalutamide as part of their management for mHSPC.
• Data Availability: Adequate baseline and follow-up data available within the RWE sources to assess the study outcomes.

Exclusion Criteria

Patients will be excluded from the study based on the following criteria:
• Insufficient Data: Incomplete or missing data that preclude the assessment of treatment outcomes.
• Other Androgen Receptor Inhibitors: Concomitant use of other androgen receptor inhibitors not within the scope of this study.
• Non-Adult Patients: Patients under the age of 18 years.
• Non-Male Patients: Since mHSPC predominantly affects males, female patients will be excluded from this study.

Identification of Participants

Participants will be identified through a systematic search of the selected RWE databases. The search will use ICD codes for prostate cancer, medication records, and other relevant clinical data to ensure accurate identification of eligible patients.

Sample Size

The sample size will be determined by the number of patients within the RWE sources who meet the inclusion criteria during the specified study period. The study aims to include a large enough sample to ensure adequate power for detecting differences in effectiveness and safety outcomes between the treatment groups.

Data Collection Period

The data collection period will encompass dates prior to the initiation of the study to ensure a comprehensive capture of eligible patients and outcomes. The specific start and end dates of the data collection period will be defined based on the availability and completeness of data within the RWE sources.

Ethical Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. Patient confidentiality will be maintained throughout the study, with data de-identified to protect personal health information.

Patient Consent

Given the retrospective nature of the study and the use of de-identified secondary data, individual patient consent may not be required. However, the study protocol will be reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) to ensure compliance with ethical standards and regulatory requirements.

Procedures

Participant Selection

Identification and Recruitment

Eligible participants will be identified through a systematic search of the selected real-world evidence (RWE) databases using specific inclusion and exclusion criteria. The search will utilize ICD codes for prostate cancer, medication records, and other relevant clinical data to ensure accurate identification of eligible patients. No direct recruitment will take place as this is a retrospective study using existing data.

Screening and Inclusion

Patients will be included if they meet the following criteria:

- Confirmed diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC).
- Received treatment with either apalutamide or enzalutamide.
- Adequate baseline and follow-up data available within the RWE sources to assess the study outcomes.

Exclusion

Patients will be excluded based on the following criteria:

- Incomplete or missing data that preclude the assessment of treatment outcomes.
- Concomitant use of other androgen receptor inhibitors not within the scope of this study.
- Patients under the age of 18 years.
- Female patients, as mHSPC predominantly affects males.

Data Collection

Data Extraction

Data will be extracted from the databases, including patient demographics, treatment details, clinical outcomes, and healthcare utilization. The data extraction process will be standardized to ensure consistency and accuracy.

Data Handling and Confidentiality

Extracted data will be de-identified and stored securely to maintain patient confidentiality. Access to the data will be restricted to authorized study personnel.

Outcome Measures

Primary Outcomes

- Overall Survival (OS): Time from initiation of treatment with apalutamide or enzalutamide to death from any cause.
- Progression-Free Survival (PFS): Time from initiation of treatment to disease progression or death from any cause, whichever occurs first.

Secondary Outcomes

- Quality-of-Life Measures: Assessment using validated instruments specific to prostate cancer and general health status.

• Adverse Events (AEs): Incidence and severity classified according to the Common Terminology Criteria for Adverse Events (CTCAE).

Exploratory Outcomes
• Subgroup Treatment Effectiveness: Effectiveness in predefined patient subgroups (e.g., age, comorbidities, prior treatments).
• Treatment Patterns: Description of treatment modifications, including dose interruptions, reductions, and discontinuations.
• Healthcare Resource Utilization: Analysis of healthcare services used during treatment, including inpatient and outpatient services, and associated costs.

Data Analysis

Comparative Effectiveness Analysis
Comparative analyses will be conducted between the apalutamide and enzalutamide cohorts using appropriate statistical methods. Propensity score matching or inverse probability of treatment weighting (IPTW) will be used to adjust for confounding factors.

Subgroup Analyses
Exploratory subgroup analyses will be performed to investigate the effectiveness and safety of apalutamide and enzalutamide across various patient demographics and clinical characteristics.

Statistical Considerations
The statistical analysis plan will detail the methods for handling missing data, defining the analysis populations, and specifying the statistical tests for each outcome measure.

Ethical Considerations

IRB Review
The study protocol will be reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) to ensure compliance with ethical standards and regulatory requirements.

Data Protection
All data will be handled in accordance with data protection laws and regulations. Patient confidentiality will be a priority throughout the study.

Study Timeline and Milestones

Data Extraction and Cleaning
The initial phase will involve data extraction and cleaning, which is expected to take approximately 2 months.

Data Analysis
Following data preparation, the analysis phase will commence, estimated to last 4 months.

Reporting and Dissemination
The final 2 months will be dedicated to interpreting the results, preparing the final report, and disseminating the findings through appropriate channels.

Safety

Adverse Event Monitoring

Definition and Classification of Adverse Events
Adverse events (AEs) will be defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) for grading the severity of adverse events.

Data Sources for Adverse Events
AE data will be extracted from secondary real-world evidence (RWE) sources, including electronic health records (EHRs) and claims databases. These sources will provide information on the incidence, severity, and types of AEs experienced by patients treated with apalutamide or enzalutamide.

Adverse Event Reporting Procedures
AEs will be reported as part of the retrospective data extraction process. The reporting will include the type of AE, onset date, duration, severity grade, outcome, and any action taken with the treatment (e.g., dose reduction, discontinuation).

Safety Analysis

Comparative Safety Profile
The safety analysis will compare the AE profiles of patients treated with apalutamide versus those treated with enzalutamide. The analysis will focus on the incidence and severity of AEs, as well as any significant differences in the types of AEs between the two treatment groups.

Statistical Methods for Safety Analysis
Descriptive statistics will be used to summarize the safety data. The incidence of AEs will be compared between the treatment cohorts using chi-square or Fisher's exact test, as appropriate. Time-to-event analyses may be conducted for serious AEs using Kaplan-Meier estimates and log-rank tests.

Subgroup Safety Analysis
Exploratory subgroup analyses will be performed to evaluate the safety of

apalutamide and enzalutamide across various patient demographics (e.g., age, comorbidities) and clinical characteristics.

Handling of Missing Data

In cases of missing AE data, the study will employ appropriate methods to handle missingness, such as multiple imputation or sensitivity analyses, to assess the impact of missing data on the safety outcomes.

Ethical Considerations

Patient Confidentiality

All patient data will be de-identified to maintain confidentiality. Only authorized study personnel will have access to the safety data.

Institutional Review Board (IRB) Oversight

The study protocol, including the safety analysis plan, will be reviewed and approved by an IRB or Ethics Committee to ensure compliance with ethical standards and regulatory requirements.

Reporting of Safety Findings

The safety findings will be reported in the final study report and disseminated to relevant stakeholders. Any significant safety concerns identified during the analysis will be communicated promptly to the medical community.

Limitations of Safety Analysis

The study acknowledges that the retrospective nature of the safety analysis using RWE sources may have inherent limitations, such as underreporting of AEs or incomplete data. These limitations will be discussed in the context of the study findings.