mone-Sensitive Prostate Cancer: A Retrospective An

Clinical Study Protocol

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"Comparative Effectiveness and Safety of Apalutamide vs. Enzalutamide in Metastatic Hormone-Sensitive Prostate Cancer: A Retrospective Analysis Using Real-World Evidence from Electronic Health Records and Claims Databases"

Data Sources

The study will utilize secondary real-world evidence (RWE) sources to conduct a comparative effectiveness analysis of apalutamide versus enzalutamide in patients with metastatic hormone-sensitive prostate cancer (mHSPC). The data sources include databases such as Flatiron Health, SEER-Medicare, and other electronic health records (EHRs) and claims databases. Each of these databases offers distinct characteristics that contribute to the robustness of the study.

Database Characteristics

1.
Flatiron Health
: This database is known for its comprehensive oncology-specific data, capturing detailed clinical information from EHRs. It includes data from a network of oncology clinics across the United States, providing insights into treatment patterns and outcomes in real-world settings.

2.
SEER-Medicare
: The Surveillance, Epidemiology, and End Results (SEER) program, linked with Medicare claims, offers a rich source of data on cancer incidence, treatment, and outcomes among the elderly population in the United States. It combines clinical cancer registry data with Medicare claims, enabling detailed analyses of healthcare utilization and outcomes.

3.
Other EHRs and Claims Databases
: Additional databases may include commercial claims databases and other EHR systems that capture a wide range of demographic, clinical, and treatment-related information.

Time Period Covered

The specific time period covered by each database will be determined based on data availability and relevance to the study objectives. [PLACEHOLDER:
Specify the time period for each database
]. It is recommended that the study covers a time frame that ensures sufficient follow-up for assessing long-term outcomes such as overall survival and progression-free survival. [RECOMMENDED:
Consider a time frame of at least 5-10 years to capture comprehensive data
].

Data Quality Assessment

The quality of data from these sources will be assessed through several measures, including completeness, accuracy, and consistency of the recorded information. Data validation processes will be implemented to ensure the reliability of extracted variables. [PLACEHOLDER:
Describe specific data quality assessment methods
]. It is recommended to conduct sensitivity analyses to evaluate the impact of potential data limitations on

study findings. [RECOMMENDED:
Implement sensitivity analyses to address data quality concerns
].

Relevant Variables Available

The databases will provide access to a range of relevant variables necessary for the study, including:

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Demographic Information
: Age, race, ethnicity, and geographic location.

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Clinical Characteristics
: Cancer stage, Gleason score, and comorbid conditions.

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Treatment Details
: Type of androgen receptor inhibitor used (apalutamide or enzalutamide), dosage, and treatment duration.

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Outcomes
: Overall survival, progression-free survival, quality of life measures, and adverse event profiles.

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Healthcare Utilization
: Hospitalizations, outpatient visits, and medication adherence.

These variables will facilitate a comprehensive analysis of the comparative effectiveness and safety profiles of apalutamide versus enzalutamide in real-world mHSPC populations.

Study Variables

Exposure Definitions

The primary exposures in this study are the treatments with androgen receptor inhibitors, specifically apalutamide and enzalutamide. Exposure is defined as the initiation of either apalutamide or enzalutamide therapy in adult male patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). The duration of exposure will be determined based on the treatment records available in the secondary real-world evidence (RWE) sources.

Outcome Measures

The primary outcome measures include:

1.
Overall Survival (OS)
: Defined as the time from initiation of treatment with either apalutamide or enzalutamide to the date of death from any cause.

2.
Progression-Free Survival (PFS)
: Defined as the time from treatment initiation to the first documented progression of disease or death from any cause, whichever occurs first.

3.
Quality of Life (QoL)
: Assessed using validated patient-reported outcome measures, if available in the data sources.

4.
Adverse Events (AEs)
: Frequency and severity of treatment-related adverse events, categorized according to the Common Terminology Criteria for Adverse Events (CTCAE).

Covariates and Confounders

The study will adjust for potential confounders that may influence treatment outcomes. These include:

- Patient demographics: Age, race, and ethnicity.

- Clinical characteristics: Baseline prostate-specific antigen (PSA) levels, Gleason score, and performance status.

- Comorbidities: Assessed using the Charlson Comorbidity Index or similar validated tools.

- Prior treatments: Previous therapies for prostate cancer, including surgery, radiation, or chemotherapy.

- Healthcare utilization: Frequency of healthcare visits and hospitalizations.

Coding Systems Used

The study will utilize standardized coding systems for data extraction and analysis, including:

- International Classification of Diseases (ICD) codes for diagnosis and comorbidities.

- National Drug Codes (NDC) for identifying specific medications.

- CTCAE for categorizing adverse events.

[PLACEHOLDER:
Additional coding systems specific to the data sources, such as LOINC for laboratory results, may be included as necessary.
]

[RECOMMENDED:
Consider incorporating additional covariates such as socioeconomic status or geographic location, if available, to further refine the analysis and adjust for potential confounding factors.
]

Analysis Approach

The analysis of the comparative effectiveness of apalutamide versus enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC) will be conducted using a structured and methodical approach to ensure robust and reliable results. The following sections outline the primary analysis methods, propensity score matching, sensitivity analyses, and missing data handling strategies.

Primary Analysis Methods

The primary analysis will focus on comparing overall survival (OS) and progression-free survival (PFS) between patients treated with apalutamide and those treated with enzalutamide. Kaplan-Meier survival curves will be generated for each treatment group, and the log-rank test will be used to assess differences in survival distributions. Cox proportional hazards models will be employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS, adjusting for potential confounders identified in the data extraction phase.

Propensity Score Matching

To address potential confounding factors and ensure comparability between treatment groups, propensity score matching (PSM) will be utilized. Patients will be matched based on a set of baseline characteristics, including age, comorbidities, disease stage, and prior treatments. The matching process will employ a nearest-neighbor algorithm with a caliper width of 0.2 standard deviations of the logit of the propensity score. Balance diagnostics, such as standardized mean differences, will be assessed to confirm the adequacy of the matching process.

Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the robustness of the primary findings. These analyses will include:

- Performing inverse probability of treatment weighting (IPTW) as an alternative method to PSM, allowing for the inclusion of all patients in the analysis while adjusting for confounders.

- Conducting subgroup analyses based on key demographic and clinical characteristics, such as age groups and baseline disease severity, to explore potential effect modifiers.

- Evaluating the impact of different definitions of progression-free survival and adverse events on the study outcomes.

Missing Data Handling

Missing data is anticipated due to the retrospective nature of the study and the use of secondary real-world evidence (RWE) sources. The following strategies will be employed to address missing data:

- Multiple imputation techniques will be applied to handle missing covariate data, assuming that data are missing at random (MAR). This approach will involve creating multiple datasets with imputed values and combining the results to obtain valid statistical inferences.

- Sensitivity analyses will be performed to assess the impact of different assumptions about the missing data mechanism, including complete case analysis and worst-case/best-case scenarios.

[PLACEHOLDER:
Specify any additional statistical methods or software to be used
]

[RECOMMENDED:
Consider conducting a validation study to assess the accuracy and reliability of the data sources used in the analysis
]

This comprehensive analysis approach is designed to provide insights into the comparative effectiveness and safety profiles of apalutamide versus enzalutamide in real-world mHSPC populations, thereby informing clinical decision-making and optimizing patient outcomes.

Study Limitations

In conducting this observational, retrospective comparative effectiveness study using secondary real-world evidence (RWE) sources, several limitations must be acknowledged to ensure the robustness and validity of the findings.

1.
Data Quality Issues

The reliance on secondary RWE sources such as electronic health records (EHRs) and claims databases introduces potential data quality issues. These sources may contain incomplete or inaccurate data entries, which could impact the reliability of the study outcomes. Variability in data recording practices across different databases may further complicate data consistency and completeness. [RECOMMENDED:
Implement rigorous data validation and cleaning procedures to enhance data quality.
]

2.
Selection Bias Considerations

Selection bias is a significant concern in observational studies, particularly when using retrospective data. The patient cohorts receiving apalutamide or enzalutamide may differ systematically in ways that influence treatment outcomes. For instance, patients with differing baseline health statuses or socio-demographic characteristics might preferentially receive one treatment over the other. [RECOMMENDED:
Utilize advanced statistical techniques such as propensity score matching or inverse probability of treatment weighting (IPTW) to mitigate selection bias.
]

3.
Confounding Factors

Confounding factors are inherent in observational studies and can obscure the true relationship between treatment and outcomes. In this study, potential confounders such as comorbid conditions, prior treatments, and healthcare access must be carefully considered. [RECOMMENDED:
Conduct sensitivity analyses to assess the impact of unmeasured confounders and adjust for known confounders using appropriate statistical methods.
]

4.
Generalizability

The generalizability of the study findings may be limited due to the specific characteristics of the data sources used. For example, databases like Flatiron Health and SEER-Medicare may not fully represent the broader population of mHSPC patients, particularly those outside the United States or those not covered by Medicare. [RECOMMENDED:
Include diverse data sources and consider stratified analyses to enhance the generalizability of the findings.

]

By addressing these limitations through methodological rigor and transparency, the study aims to provide valuable insights into the comparative effectiveness of apalutamide versus enzalutamide in real-world settings, thereby informing clinical decision-making and improving patient care.