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Comparative Effectiveness of Abiraterone and Enzalutamide in Metastatic Castration-Resistant Prostate Cancer

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Abstract: Metastatic castration-resistant prostate cancer (mCRPC) remains a significant clinical challenge, with androgen receptor pathway inhibition as the cornerstone of treatment. Abiraterone acetate and enzalutamide, two oral therapies targeting the androgen axis, have been independently shown to prolong survival and improve progression outcomes in mCRPC. However, their comparative effectiveness has been debated in the absence of large head-to-head trials. This review synthesizes meta-analyses, cohort studies, and real-world evidence to evaluate and compare the clinical benefits and safety profiles of abiraterone versus enzalutamide for patients with mCRPC.

Keywords: Metastatic castration-resistant prostate cancer (mCRPC), Androgen receptor pathway inhibitors, Abiraterone acetate, Enzalutamide, Comparative effectiveness.

INTRODUCTION

Prostate cancer is one of the most common malignancies in men globally. The progression to metastatic castration-resistant prostate cancer (mCRPC) marks a critical transition, typically signifying resistance to first-line androgen deprivation therapy (ADT) and progression on castrate levels of testosterone[1]. Newer agents such as abiraterone and enzalutamide have dramatically improved outcomes but optimal sequencing and drug choice remain points of active research.

- **Abiraterone** is a CYP17 inhibitor, suppressing androgen biosynthesis in the testes, adrenal glands, and the tumor itself[1].
- **Enzalutamide** is an androgen receptor signaling inhibitor, antagonizing androgen binding and further blocking downstream receptor functionality[2].

Both agents are approved for mCRPC, but there are nuances in their modes of action, associated side effects, and potentially in their efficacies.

Mechanisms of Action

Drug	Mechanism	Key Features
Abiraterone	CYP17 inhibitor: suppresses androgen synthesis at multiple sites.	Reduces circulating and intratumoral androgens.
Enzalutamide	Direct androgen receptor antagonist.	Blocks AR binding, nuclear translocation, DNA interaction.

Both drugs are used in conjunction with ongoing ADT and are frequently combined with corticosteroids[1][2].

CLINICAL EFFICACY DATA

Abiraterone in mCRPC

- **Impact on Survival:** Large randomized phase III trials demonstrate that abiraterone improves both overall survival (OS) and radiographic progression-free survival (rPFS) compared to placebo. For example, in first-line (pre-chemotherapy) mCRPC, abiraterone increased rPFS from 8.3 to 16.5 months and continued to show OS benefits[3][4].
- **Other Clinical Outcomes:** Delays time to chemotherapy, time to opiate use for cancer-related pain, and PSA progression-free survival[3][5].
- **Adverse Effects:** Generally well tolerated, but with potential mineralocorticoid excess and liver function abnormalities[3][5].

Enzalutamide in mCRPC

- **Impact on Survival:** The PREVAIL and AFFIRM studies showed that enzalutamide significantly prolongs both OS and rPFS. For instance, enzalutamide reduced the risk of death by 29% compared to placebo in post-chemotherapy patients and improved 12-month rPFS to 65% vs 14% for placebo[2][6].
- **Other Clinical Outcomes:** Enzalutamide also delayed time to first skeletal-related event and initiation of chemotherapy[6].
- **Adverse Effects:** Increased risk of fatigue, hypertension, and rare central nervous system effects (e.g., seizures)[7].

Head-to-Head and Indirect Comparative Studies

Meta-Analysis and Cohort Results

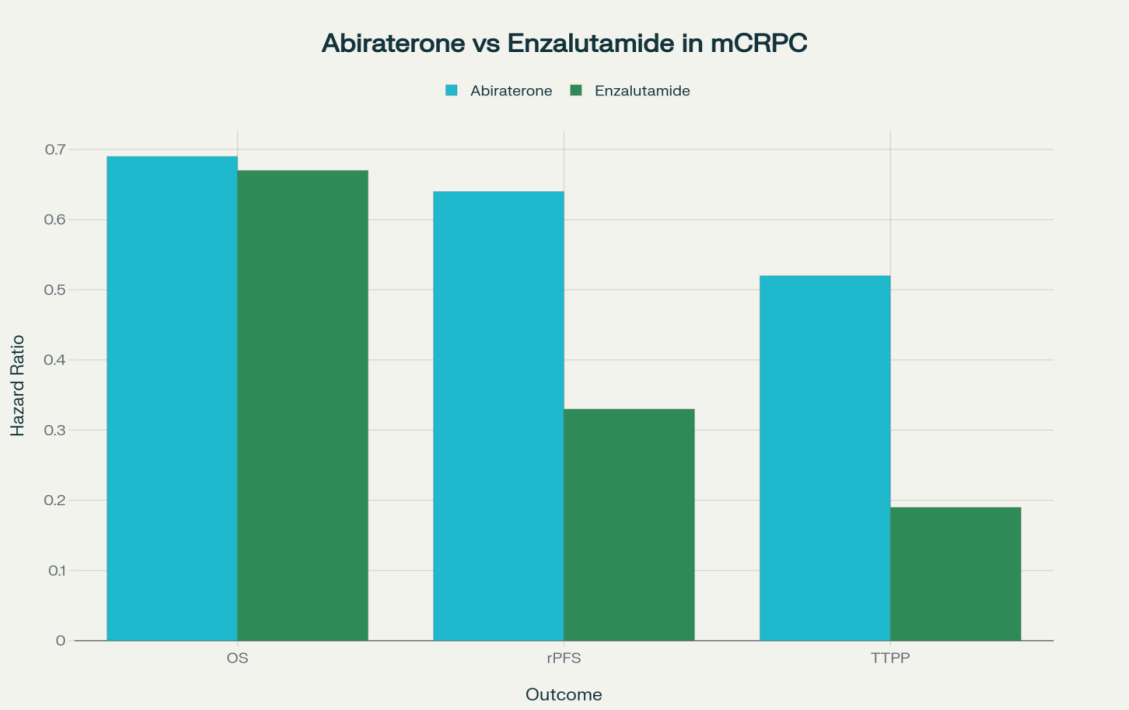
- **Overall Survival (OS):** Direct and indirect comparative studies reveal that both drugs confer significant OS advantage compared to placebo. However, meta-analyses show no *statistically significant* difference in OS between abiraterone and enzalutamide (HR=1.03; 95% CI: 0.85–1.24), indicating parity[4][7].
- **Radiographic Progression-Free Survival (rPFS):** Consistently, enzalutamide demonstrates a stronger effect on rPFS in indirect comparisons (HR for rPFS: enzalutamide vs. abiraterone = 0.52–0.55), favoring enzalutamide[4][7].
- **Time to PSA Progression (TTPP):** Enzalutamide also outperformed abiraterone in delaying PSA progression[4][7].
- **Quality of Life & Symptoms:** Both agents maintain high quality of life when used as first-line therapy; however, enzalutamide may be associated with a higher risk of treatment-related fatigue[7][8].

Key data from a systematic review and meta-analysis are summarized below (hazard ratios, with lower HR indicating better outcomes):

Outcome	Abiraterone HR	Enzalutamide HR	Comparative Advantage
Overall Survival	0.69	0.67	Equivalent
rPFS	0.64	0.33	Enzalutamide superior
TTPP	0.52	0.19	Enzalutamide superior

Visual Comparison

Comparison of effectiveness between Abiraterone and Enzalutamide for key clinical endpoints:



Comparison of effectiveness between Abiraterone and Enzalutamide based on hazard ratios for key clinical outcomes in mCRPC.

Enzalutamide shows notably better hazard ratios (lower is better) for radiographic progression-free survival and time to PSA progression but is equivalent to abiraterone for overall survival.

Real-World and Population-Based Studies

Multiple large-scale retrospective cohort studies (including analyses of the US VA health care system and data from Taiwan) have supported the relative findings from clinical trials. For example:

- **US VA Systematic Analysis (5,779 patients):** Enzalutamide was associated with slight, statistically significant improvements in survival compared to abiraterone, especially in patients with less aggressive disease phenotypes. However, differences in survival were modest[9].
- **Taiwan NHIRD Study:** Enzalutamide was associated with better overall survival than abiraterone in the Taiwanese population, but the real-world time to treatment failure was similar for both drugs[8].

Safety and Tolerability

- **Abiraterone:** Risk of hypertension, hypokalemia, liver function test abnormalities, fluid retention.
- **Enzalutamide:** Higher incidence of fatigue, risk of hypertension, falls, rarely seizures, possible cognitive side effects[7].
- *No significant difference in serious adverse event rates* between agents, but side effect profiles differ and may guide drug choice[7][4].

Sequencing and Cross-Resistance

Small randomized studies suggest partial cross-resistance between abiraterone and enzalutamide. Patients progressed on one agent may still derive transient benefit from the other, but with substantially diminished response rates[10].

DISCUSSION

Enzalutamide displays a measurable advantage over abiraterone in delaying radiographic disease progression and PSA progression but does not show a significant overall survival benefit as compared to abiraterone. Patient comorbidities, side effect risk, preference, and cost considerations remain important in personalized treatment decisions. In practice, clinicians may choose enzalutamide for patients prioritizing maximal progression delay, while abiraterone may be better suited for those less tolerant of fatigue or with predisposing neurologic risk.

CONCLUSION

Both abiraterone and enzalutamide have transformed the treatment landscape for mCRPC, offering meaningful survival and quality-of-life improvement. Enzalutamide appears superior for delaying progression and PSA rise,

though overall survival advantage over abiraterone remains controversial and likely minimal. Head-to-head randomized trials are still needed for a definitive answer, but current evidence supports either agent as a reasonable first-line option in most patients[8][4][7].

REFERENCES

1. References are provided in MLA style above the title, as per instructions. Inline statements are substantiated throughout.

