

# Efficacy and Safety of Enzalutamide in Metastatic Prostate Cancer Patients: A Systematic Review and Meta-analysis

Rashid M, Shamshavali K, Vsn M, Hyderboini RK, Thode R, Namare S, Belekar V, Chakrawarthy M, Dang A  
MarksMan Healthcare Communications, HEOR, Scientific Outsourcing and Research Consulting, India

## INTRODUCTION

- Prostate cancer is the second most common cancer in the world and the sixth leading cause of cancer death in men across the world.<sup>1</sup>
- An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, and the new cases of prostate cancer are expected to rise to 1.7 million with 499,000 new deaths by 2030.<sup>1</sup>
- Enzalutamide (ENZ) is an oral drug and inhibitor of androgen-receptor (AR) that prolongs the survival in men with castration-resistant metastatic prostate cancer (CRPC).<sup>2,3</sup>
- ENZ binds AR competitively to prevents the translocation of AR from the cytoplasm to the nucleus. It also inhibits AR binding to chromosomal DNA to prevent the transcription of tumor genes within the nucleus.<sup>4</sup>
- Unlike other treatments for prostate cancers, ENZ does not require administration of the drug with steroids.<sup>4</sup>

## OBJECTIVE

- To evaluate the efficacy and safety of ENZ versus placebo in metastatic prostate cancer patients (mPCa).

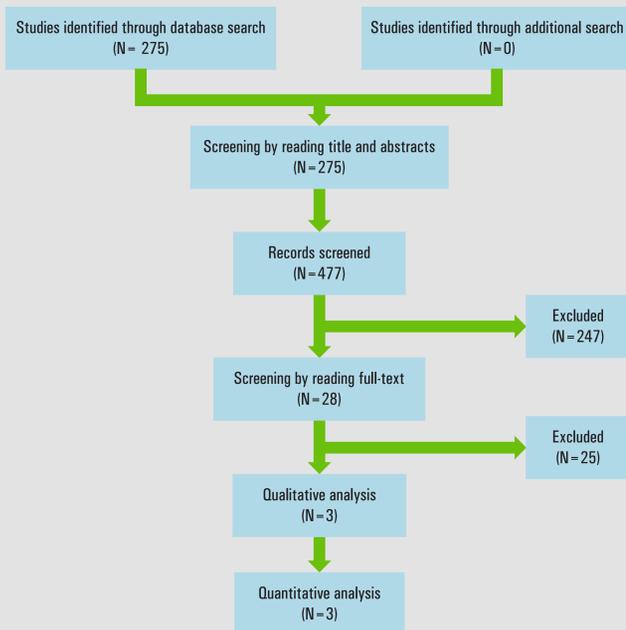
## MATERIALS AND METHODS

- Literature searches were conducted in MEDLINE and the Cochrane Library. In addition, references of included studies and clinicaltrials.gov were searched for relevant studies. No language or date restrictions were imposed.
- Two authors independently selected the articles, extracted the data and assessed the quality of included studies. Disagreements were resolved by discussion or by consulting another author.
- Study quality of the included trials was assessed using the Cochrane Risk of Bias Assessment Tool.

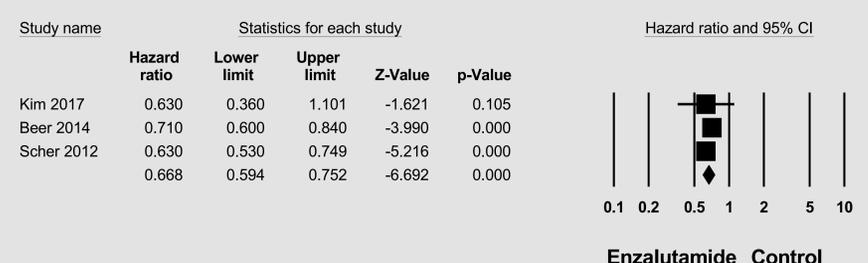
### Outcomes:

- Primary: overall survival (OS) and progression-free survival (PFS).
- Secondary: objective response (OR), any grade adverse events (AE) and overall treatment discontinuation (OTD).
- All randomized controlled trials (RCTs) examined for the efficacy and safety of ENZ compared to placebo in mPCa patients were included.

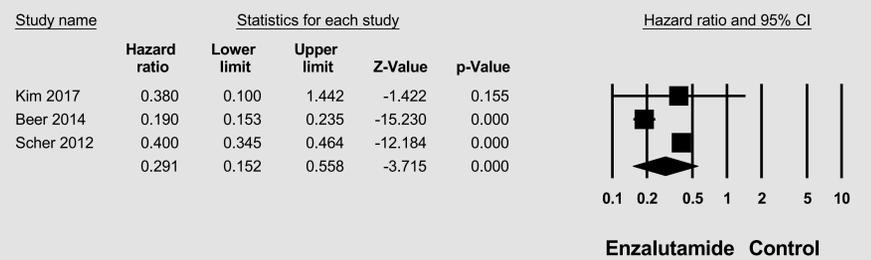
## RESULTS



- A total of 3 RCTs with 3063 patients were included in the study.
- The number of patients receiving ENZ were 1745, and those receiving placebo were 1318.
- ENZ showed significantly better OS and radiographic PFS with improved OR as compared to placebo.
- There was no significant difference between the groups in terms of any grade AEs (Risk ratio [RR]=1.03, 95% confidence interval [CI] 0.99-1.08). However, the OTD with ENZ was lesser compared to placebo.
- Overall, the risk of bias of the included trials was unclear (N=2) to high (N=1).
- The most common AEs with ENZ were fatigue, back pain, arthralgia, constipation, and hot flash.



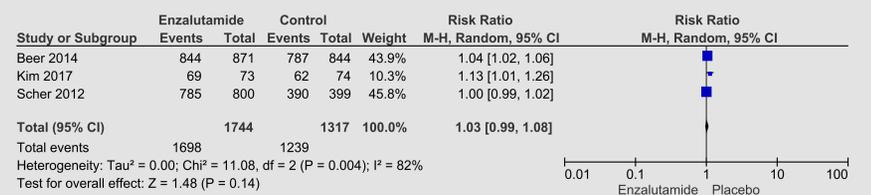
The OS of ENZ was higher as compared to placebo (Hazard Ratio [HR] 0.668, 95% CI 0.5940.752)



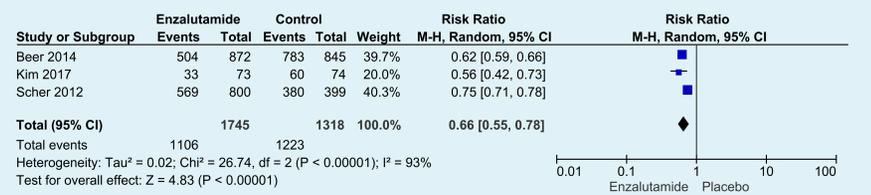
The radiographic PFS of ENZ was higher as compared to placebo (HR 0.291;; 95% CI 0.1520.558)



ENZ showed improved OR compared to placebo (Risk Ratio [RR]=9.81, 95% CI 6.9913.77, N=1579)



There was no significant difference in any grade AE between ENZ and placebo (RR=1.03, 95% CI 0.99-1.08, N=3061)



The OTD of ENZ was lesser as compared to placebo (RR=0.66, 95% CI 0.55-0.78, N=3063)

## DISCUSSION

- Enzalutamide is an AR inhibitor that targets several steps in the AR signaling pathway and has shown significant efficacy in the treatment of CRPC in patients with or without prior chemotherapy.
- It is a non-steroidal second-generation anti-androgen that has been approved for the treatment of CRPC both in the post-docetaxel and chemotherapy-naïve settings.
- The PREVAIL trial showed that ENZ significantly reduced the risk of radiographic PFS by 81% and risk of death by 29% as compared to placebo. It was found to be well tolerated and showed lower incidence of grade 3 or greater AEs as compared to placebo (45.3% vs. 53.1%) in long-term therapy.<sup>2</sup>
- The randomized, double-blind phase III AFFIRM trial demonstrated that ENZ significantly prolonged OS [median 18.4 versus 13.6 months (hazard ratio, HR) 0.63 (95% confidence interval, CI, 0.53-0.75); P < 0.001] compared with placebo in patients with CRPC who received prior docetaxel chemotherapy. Time to prostate-specific antigen (PSA) progression was 8.3 vs 3.0 months, the proportion of patients with a reduction in the PSA level by 50% or more was 54% vs 2%, the quality-of-life response rate was 43% vs 18%, and the time to first skeletal-related event was 16.7 vs 13.3 months in ENZ group as compared to placebo.<sup>3,4</sup>
- ENZ treatment was found to be associated with better health-related quality of life in several domains as compared to bicalutamide in asymptomatic/mildly symptomatic CRPC.<sup>5</sup>
- Treatment effect and safety of ENZ has been found to be consistent in East Asian patients, while comparing the results with the PREVAIL study.<sup>6</sup>

## CONCLUSION

ENZ is associated with significant improvement in OS, PFS, and OR with lesser OTD as compared to placebo in mPCa patients. Our analysis suggests that it is safe and efficacious drug with tolerable side effects. Further analysis on more RCTs with adequate power is needed to support the current finding.

## REFERENCES

- Jain S et al. Meta Gene 2014; 2:596-605
- Beer TM et al. N Engl J Med 2014; 371 (5): 424-433
- Scher HI et al. N Engl J Med 2012; 367 (13): 1187-1197
- Saad F Ther Adv Uro 2013; 5(4):201-210
- Heidenreich A et al. Eur Urol. 2017; 71(4):534-542
- Kim CS et al. Medicine 2017; 96:27(e7223)