01. Title: Precision Targeting in Metastatic Castration-Resistant Prostate Cancer

Ali hassan salim kidiya[1], Arshiya ummey[2], Naga Sai Gouthami Gurujala[3], Srijamya[4]

[1] Intern, Dr. B. R Ambedkar Medical college and hospital
[2] Medical Student, University Of Perpetual Help System DALTA, Philippines
[3] Medical graduate, Nri Medical College, India
[4] MD. ASMC, Lakhimpur Kheri, Uttar Pradesh, India.

Background: Castration-resistant prostate cancer continues to be an incurable and aggressive condition. Enzalutamide; an antiandrogen, shows better radiographic progression-free survival and overall survival in men with metastatic castration-resistant prostate cancer and reduces risk of progression or death by 68%. Gene EZH2 activity in prostate cancer is linked to promote progression and resistance to hormone therapies. Mevrometostat targets this EZH2 gene. Therefore, this combination can be beneficial to maximise the results.

Objective: To explore the safety and efficacy of mevrometostat (PF-06821497), an LSD1 inhibitor, combined with enzalutamide in patients with metastatic castration-resistant prostate cancer who have progressed after prior androgen receptors–targeted therapy.

Methodology: A randomized open label, phase 3 trial was conducted in patients with metastatic castration resistant prostate cancer. The primary aim of the study is to evaluate the Radiographic Progression free Survival. The secondary targets include overall survival, time to pain progression, pharmacokinetics, ct DNA and patient-reported outcomes.

Results: In the randomized dose-expansion cohorts, 81 patients were assessed (41 received mevrometostat combined with enzalutamide, while 40 were given enzalutamide alone). The baseline characteristics were similar (median age around 70 years; ECOG performance status of 0-1, many had prior abiraterone treatment). The median radiographic progression-free survival (rPFS) was 14.3 months (95% CI, 7.5-Non Estimable) for the combination of mevrometostat and enzalutamide, compared to 6.2 months (95% CI, 4.1-13.9) for enzalutamide alone (hazard ratio 0.51; 90% CI, 0.28-0.95), suggesting a roughly 49% reduction in the radiological progression and risk of death with an average follow-up of about 9.6 months.

Conclusion: Dual EZH2 and AR inhibition in metastatic castration prostate cancer with mevrometostat and enzalutamide shows synergism in overcoming resistance and improving therapeutic outcomes through activating the immune pathways.

Key Words: Castration-resistant prostate cancer, Mevrometostat, EZH2 gene, pharmacokinetics, AR inhibition.

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