Matching-Adjusted Indirect Comparison of the Efficacy of Apalutamide and Enzalutamide in the Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

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Introduction and Objectives

- Apalutamide and enzalutamide are new generation non-steroidal anti-androgen treatment options for nonmetastatic castrate-resistant prostate cancer (nmCRPC) with the aim of delaying progression to metastasis
- Both drugs have been studied in separate randomized placebo-controlled clinical trials, but have not been directly compared[1,2]
- The study compared efficacy of apalutamide and enzalutamide with respect to metastasis-free survival (MFS), overall survival (OS), and health-related quality of life using matching-adjusted indirect comparison (MAIC)

Methods

Data Source

- Individual patient-level data (IPD) from the SPARTAN trial (apalutamide) and published data from the PROSPER trial (enzalutamide) were utilized

Endpoints

- MFS was defined differently in the two trials. This study used the definition from the PROSPER (i.e., time from randomization to radiographic progression or death within 112 days of treatment discontinuation)
- Health-related quality of life was evaluated using the Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) scores; baseline and follow-up (week 97 for PROSPER and week 96 for SPARTAN) values were used

Statistical Analyses

- MAIC was conducted by reweighting IPD from the SPARTAN to resemble baseline characteristics of patients in the published aggregate data from the PROSPER
- Hazard ratios (HR) for MFS and OS, and least square (LS) differences for the FACT-P scores were re-estimated for the reweighted SPARTAN population, and indirectly compared to those in the PROSPER using a Bayesian network meta-analysis (NMA)

Results: Baseline Characteristics

- Prior to matching, SPARTAN and PROSPER patient populations differed with respect to % patients with PSADT<6 months, median PSADT, serum PSA at baseline, and PSADT (**Table 1**)
- After matching, baseline characteristics were balanced between the two trials

Table 1. Baseline Characteristics and Matching Results

	PROSPER	SPARTAN	SPARTAN MAIC-weighted[1]
	N=1,401	N=1,207	N=1,171
Median age, years	73.70	74.00	74.00
% Age <75	0.54	0.52	0.54
Median serum PSA at baseline (ng/mL)	10.80	7.80	10.80
Median PSADT (months)	3.70	4.40	3.70
% PSADT <6 months	0.77	0.70	0.77
% ECOG score =1	0.19	0.23	0.19
% Total Gleason score 2-4	0.02	0.02	0.02
% Total Gleason score 5-7	0.54	0.55	0.54
% Total Gleason score 8-10	0.44	0.44	0.44
% Surgical prostate cancer procedures: yes	0.54	0.57	0.54
% Use of bone targeting agent	0.11	0.10	0.11

MAIC: matching adjusted indirect comparison; ECOG: Eastern Cooperative Oncology Group Performance Status; PSA: prostate-specific antigen; PSADT: PSA doubling time

Note:
1. Weights were obtained by matching on the baseline characteristics from the PROSPER trial. The effective sample size was 1,049; 36 patients were excluded from SPARTAN as information on at least one matching criterion was missing

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Results: MFS, OS, and Health-Related Quality of Life

MFS

- MFS was similar in SPARTAN before and after reweighting (**Table 2**)
- MAIC results suggested a more favorable MFS (probability of 73.6%) with apalutamide vs enzalutamide (**Table 3**)

OS

- OS in the SPARTAN improved after reweighting and reached statistical significance (**Table 2**)
- MAIC results suggested a more favorable OS (probability of 83.5%) with apalutamide vs enzalutamide (**Table 3**)

Health-Related Quality of Life

- Results in the SPARTAN improved slightly after reweighting (**Table 2**)
- MAIC results suggested a more favorable change in FACT-P (probability of 73.1%) for apalutamide relative to enzalutamide. Differences were most pronounced on physical and functional wellbeing, and pain-related sub-scale (**Table 3**)

Strength and Limitations

- The strengths of these study include adjustment for differences in patient characteristics between the two trials and the use of the Bayesian approach, which is better suited for decision making
- The limitation of this study is that although potential bias was substantially reduced after matching, residual bias due to unobserved patient characteristics may exist.

Conclusions

- Based on MAIC results, nmCRPC patients treated with apalutamide have a more favorable MFS, OS and health-related quality of life vs patients treated with enzalutamide

References

1. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. The New England Journal of medicine. 2018; 378(26):2465-2474
2. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer. The New England Journal of Medicine. 2018

Table 2. SPARTAN Results: Original vs Matched for PROSPER Characteristics (Apalutamide vs Placebo)

	Original	MAIC-weighted
	HR [95% CI]	
MFS	0.27 [0.22; 0.33]	0.26 [0.21; 0.33]
OS	0.70 [0.47; 1.04]	0.62 [0.41; 0.94]
	LS mean difference [95% CI]	
FACT-P	3.34 [-0.23; 6.91]	3.53 [-0.18; 7.24]
FACT-G	2.52 [-0.22; 5.26]	2.87 [0.01; 5.73]
PCS	0.81 [-0.46; 2.07]	0.90 [-0.42; 2.21]
PWB	0.83 [-0.00; 1.66]	0.86 [0.00; 1.71]
SWB	1.47 [0.36; 2.58]	1.53 [0.38; 2.69]
FWB	0.76 [-0.37; 1.89]	0.98 [-0.20; 2.15]
EWB	0.50 [-0.31; 1.31]	0.44 [-0.40; 1.27]
PCSP	0.87 [0.14; 1.60]	0.76 [0.00; 1.52]
FAPSI	0.92 [-0.00; 1.85]	0.92 [-0.04; 1.89]
TOI	1.87 [-0.72; 4.47]	2.00 [-0.69; 4.70]

Table 3. MAIC Results (Apalutamide vs Enzalutamide)

	HR [95% CrI]	p(HR<1)
MFS	0.91 [0.68; 1.22]	73.6%
OS	0.77 [0.46; 1.30]	83.5%
	LS mean difference [95% CrI]	**p(diff>0)**
FACT-P	1.50 [-3.27; 6.27]	73.1%
FACT-G	1.62 [-2.03; 5.28]	80.7%
PCS	0.20 [-1.48; 1.88]	59.0%
PWB	1.12 [-0.01; 2.25]	97.3%
SWB	0.60 [-0.87; 2.07]	78.7%
FWB	0.85 [-0.64; 2.34]	86.7%
EWB	0.10 [-0.96; 1.15]	57.0%
PCSP	0.63 [-0.33; 1.59]	90.1%
FAPSI	0.48 [-0.77; 1.75]	77.3%
TOI	1.25 [-2.22; 4.72]	75.9%

CI: confidence interval; CrI: credible interval; EWB: Emotional Wellbeing; FACT-P: Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI: FACT Advanced Prostate Symptom Index; FWB: Functional Wellbeing; HR: hazard ratio; LS: least square; MAIC: matching adjusted indirect comparison; MFS: metastatic free survival; OS: overall survival; PCS: Prostate Cancer Subscale; PCSP: PCS Pain Score; PWB: Physical Wellbeing; SWB: Social Wellbeing; TOI: Trial Outcome Index