The Performance of Anchored and Unanchored Population Adjustment Methods (Matching-Adjusted Indirect Comparison, Simulated Treatment Comparison, and Multiple Imputation Marginalization) in Metastatic Castration-Resistant Prostate Cancer

MSR39

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BACKGROUND

- Population-adjusted indirect comparisons are becoming increasingly popular in health technology assessments, particularly with single-arm trials. So far, limited research has been conducted to validate these methods.
- This research compares abiraterone, using individual patient-level data (IPD) from the COU-AA-301 trial,[1] with enzalutamide, using summary data from the AFFIRM trial,[2] in metastatic castration-resistant prostate cancer with prior chemotherapy. These trials had nearly identical inclusion criteria, and both included placebo as the control arm. However, overall survival in both treatment arms was poorer in COU-AA-301 compared with AFFIRM. The reported relative treatment effects versus placebo in both trials suggests these treatments are equivalent (hazard ratios [HRs], 0.66 in COU-AA-301 and 0.63 in AFFIRM).

OBJECTIVE

- This research aimed to compare the performance of population adjustment methods in anchored (2 trials with a common comparator arm) and unanchored settings (a comparison of 2 unconnected studies).

METHODS

- The following population adjustment methods were conducted:
  - **Matching-adjusted indirect comparison (MAIC)[3]:** A propensity score weighting method.
  - **Simulated treatment comparison (STC)[3]:** A regression-based method. In the anchored setting, a Cox model was fitted; in the unanchored setting, a parametric survival model was fitted with an exponential distribution.
  - **Multiple imputation marginalization (MIM)[4]:** Survival models were fitted to the IPD and model parameters simulated. Then multiple imputation of the entire covariate data was conducted that matched the target population. Survival data were then simulated for the imputed data and re-censored to match the original trial. Marginal models were then fitted to estimate the treatment effect. This was conducted for a range of non-stratified and stratified parametric models and spline-based models, with model averaging used to produce the results.
- For the anchored STC and MIM, main effects were included with treatment interactions added where the main effects were significant ($P < 0.05$) and interaction effects had a P value of < 0.5, which resulted in age and Eastern Cooperative Oncology Group (ECOG) ≥ 2 interactions being added.
- To evaluate the performance of these methods, the HRs were estimated for abiraterone versus enzalutamide. The correct answer was assumed to be close to 1.0 due to the comparable HRs reported from both trials.

RESULTS — ANCHORED COMPARISON

- Table 1 presents the baseline patient characteristics.
  - Only small differences between the trials were observed.

Table 1. Baseline Patient Characteristics

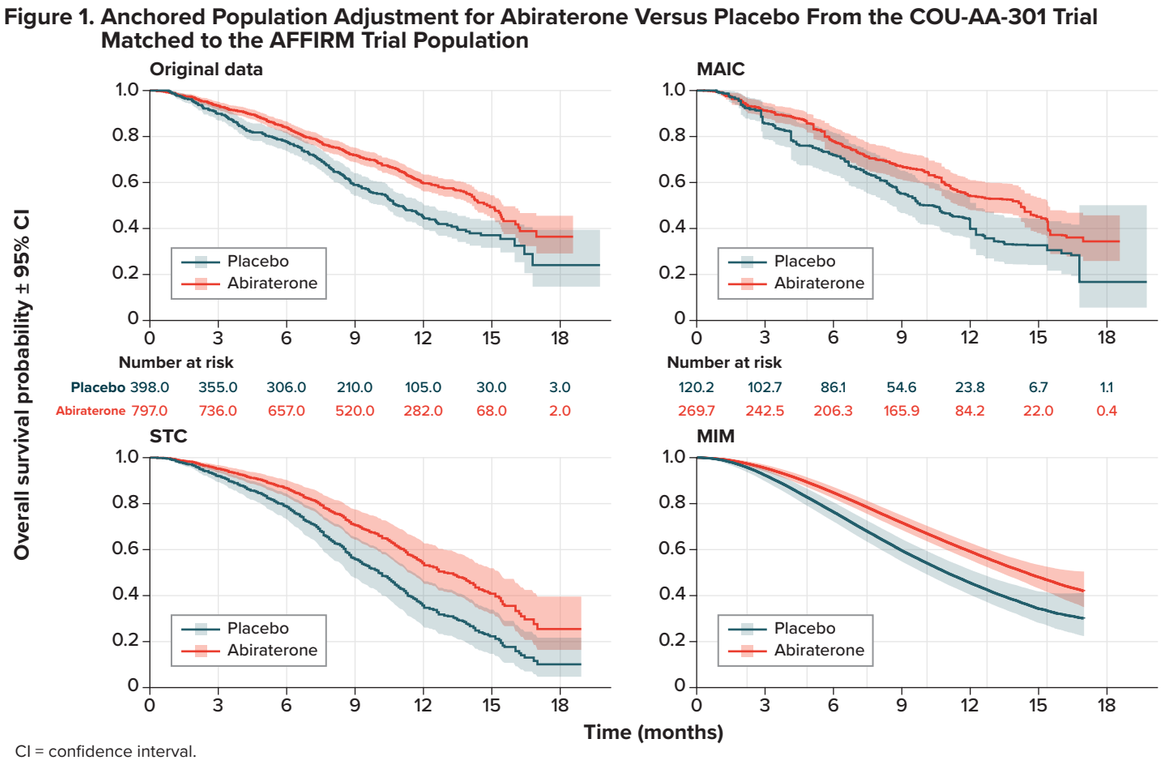
	COU-AA-301[1]			AFFIRM[2,5]		
	Placebo	ABIR	All	Placebo	ENZAL	All
Sample size	398	797	1,195	399	800	1,199
Age (years)[a]	69	69	69	69	69	69
Alkaline phosphate (U/L)[a]	**143**	**134**	**137**	108	115	113
Hemoglobin (g/dL)[a]	11.9	11.7	11.8	12.0	12.0	12.0
LDH (U/L)[a]	**240**	**225**	**230**	215	209	211
Prostate-specific antigen (ng/mL)[a]	**135**	**125**	**128**	128	108	115
Serum albumin (g/dL)[a]	4.1	4.0	4.1	3.8	3.8	3.8
Years since diagnosis[a]	5.65	6.69	6.35	6.00	**5.90**	5.93
ECOG ≥ 2[b]	0.11	0.10	0.11	0.08	0.09	0.09
Liver metastases[b]	0.08	0.11	0.10	0.09	0.12	0.11
Pain ≥ 4[b]	0.26	0.24	0.25	**0.29**	**0.28**	**0.28**
Previously received ≥ 2 chemotherapies[b]	0.28	0.28	0.28	0.26	0.28	0.27
Radiographic progression[b]	0.66	0.67	0.67	0.59	0.59	0.59
Visceral metastases[b]	0.25	0.32	0.30	0.23	0.27	0.26

Note: **Red shading** highlights differences where a variable was associated with a numerical increase in the HR, although no differences were significant.

ABIR = abiraterone; ENZAL = enzalutamide; LDH = lactate dehydrogenase.
[a] Median.
[b] Proportion.

- LDH, years since diagnosis, serum albumin, ECOG, and age, were found to be important prognostic factors. There was little evidence of treatment-effect modifiers.
- Figure 1 presents results from the anchored comparison.
  - MAIC, STC, and MIM show the same pattern as the original data from COU-AA-301, with abiraterone having significantly better survival compared with placebo.

Figure 1. Anchored Population Adjustment for Abiraterone Versus Placebo From the COU-AA-301 Trial Matched to the AFFIRM Trial Population



CI = confidence interval.

- Table 2 presents HRs from the anchored indirect comparison.
  - All models gave similar results, with MIM being closest to the original data in terms of both the point estimates and 95% CIs; all indicated abiraterone is equivalent to enzalutamide.

Table 2. Hazard Ratios From Anchored Comparisons for Abiraterone Versus Placebo and Abiraterone Versus Enzalutamide

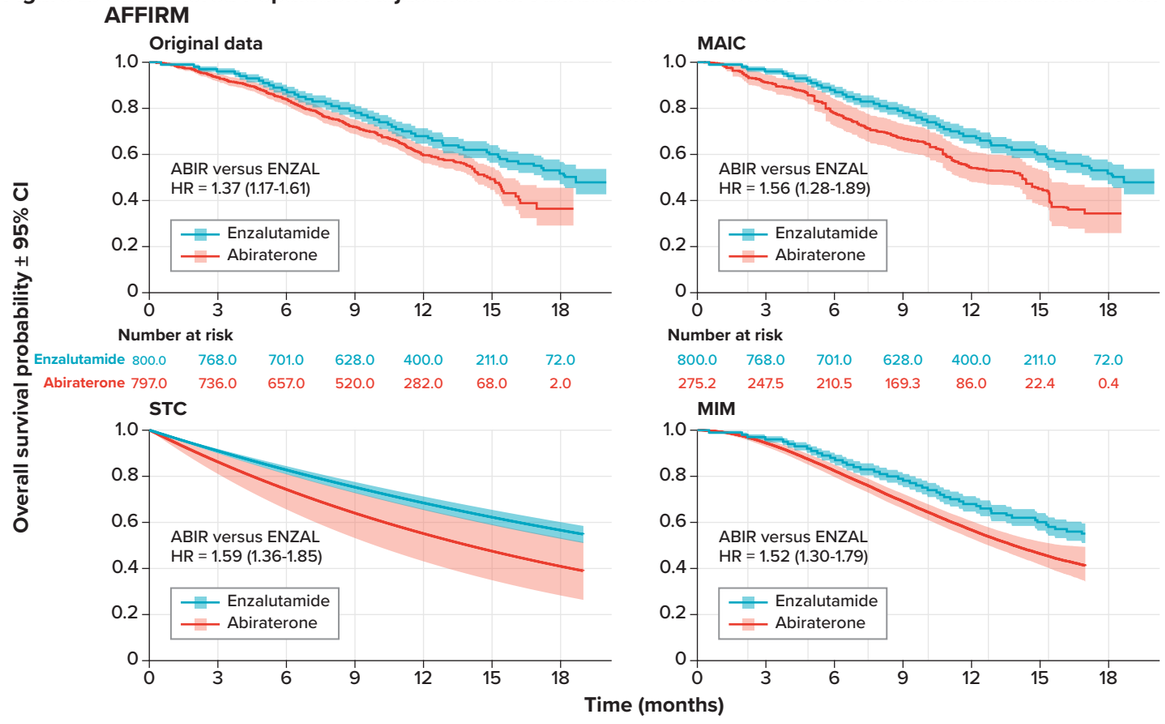
	ABIR vs. placebo			ABIR vs. ENZAL		
	HR	Lower	Upper	HR	Lower	Upper
Original data	0.67	0.56	0.79	1.06	0.83	1.35
MAIC	0.69	0.51	0.93	1.09	0.77	1.55
STC	0.61	0.51	0.73	0.97	0.75	1.25
MIM	0.66	0.56	0.79	1.05	0.82	1.34

Lower = lower 95% CI; Upper = upper 95% CI.
Note: Reported HR for enzalutamide vs, placebo: 0.63 (0.53-0.75).

RESULTS — UNANCHORED COMPARISON

- Figure 2 presents results from the unanchored comparison.
  - These charts suggest that abiraterone is significantly poorer compared with enzalutamide.
  - None of the population adjustment methods improved upon the results from the naïve comparison; all suggest abiraterone is significantly poorer compared with enzalutamide. The expectation is that there is no difference given results from the indirect treatment comparison from all analyses performed under the anchored setting.

Figure 2. Unanchored Population Adjustment for Abiraterone From COU-AA-301 Versus Enzalutamide From AFFIRM



Note: 95% CIs are in parentheses.

DISCUSSION

- In the anchored setting, the population adjustment methods performed well, although there was no evidence of treatment-effect modifiers in this example.
- In the unanchored setting, the population adjustment methods performed poorly.
  - The results suggest that there are unknown prognostic factors. These may include genetic and/or socioeconomic differences in the trial populations. The only information reported on geographic regions from the 2 trials was the following:
    - COU-AA-301: 147 sites in United States, Europe, Australia, and Canada
    - AFFIRM: 156 sites in 15 countries
  - Population adjustment methods with single-arm data assume patients are sampled at random and are uncorrelated. If patients are correlated, such as within country and sites, the effective sample may be much lower than the sample size assumed by these methods.

CONCLUSIONS

- In an anchored setting, population adjustment methods may be a useful tool when there is evidence and/or clinical reason to suspect treatment-effect modifiers exist.
- In an unanchored setting, it may not be possible to perform a robust analysis unless country differences are considered. This information is typically not reported in clinical trials. Therefore, even where all known prognostic factors are reported for the aggregate data and are available in the IPD dataset, a control arm is needed to estimate a relative treatment effect.

ACKNOWLEDGEMTS

This study, carried out under Yale University Open Data Access (YODA) Project #2022-5039, used data obtained from the YODA Project, which has an agreement with Janssen Research & Development, LLC. The interpretation and reporting of research using these data are solely the responsibility of the author and do not necessarily represent the official views of the YODA Project or Janssen Research & Development, LLC.

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