EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Matching-Adjusted Indirect Comparison of the Efficacy and Tolerability of Apalutamide vs Enzalutamide for the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer

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"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Background

- Nonmetastatic castration-resistant prostate cancer (nmCRPC) is a prostate cancer disease stage defined by progression on ADT without radiographic evidence of distant tumors with conventional imaging techniques
- Apalutamide and enzalutamide are both treatments for nmCRPC

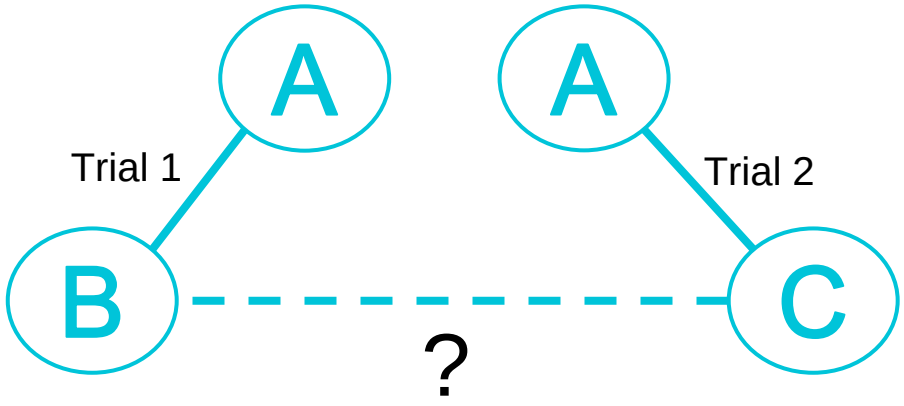
Phase 3, randomized, PBO-controlled studies:	SPARTAN:	APA + ADT	vs	PBO + ADT
	PROSPER:	ENZA + ADT	vs	PBO + ADT

- A head-to-head study of APA + ADT vs ENZA + ADT has not been conducted

Study Objective

- To compare the efficacy, tolerability and health-related quality of live of APA + ADT and ENZA + ADT based on results of SPARTAN and PROSPER

Indirect treatment comparison (ITC)



- Ideal solution: A randomized clinical trial (RTC) between B and C!
- However,... RCTs are time consuming and costly!
- Is there another option?

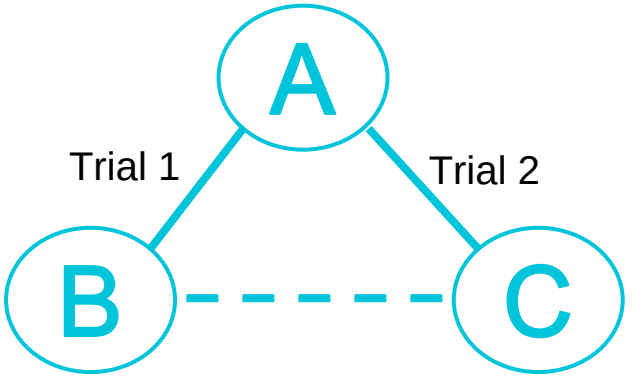
How to compare treatments from different trials?

		TRIAL 2	
		Individual patient level data (IPD)	**Summary data (AD)**
TRIAL 1	**Individual patient level data**	• Regression analysis • PS weighting or matching • …	• ANCHORED MAIC or STC unbalanced pop. • UNACHORED MAIC or STC single arm/no anchor • ML-NMR
	Summary data	• ANCHORED MAIC or STC unbalanced pop. • UNACHORED MAIC or STC single arm/no anchor • ML-NMR	• ITC (Bucher) • NMA • Meta-regression • …

AD: aggregate level data; PS: propensity score; ITC: indirect treatment comparison; NMA: network meta-analysis; MAIC: matching adjusted indirect; comparison; STC: simulated treatment comparison; ML-NMR: multilevel network meta-regression

NMA

- MAIN ASSUMPTION: Populations have to be similar with respect to all treatment effect modifiers (TEM)
  - Imbalance in prognostic patient characteristics is not an issue because we compare relative treatment effects vs a common comparator
  - If there is an imbalance in patient of study characteristics that influence the treatment effect on outcome (TEM), results of an NMA can be biased!



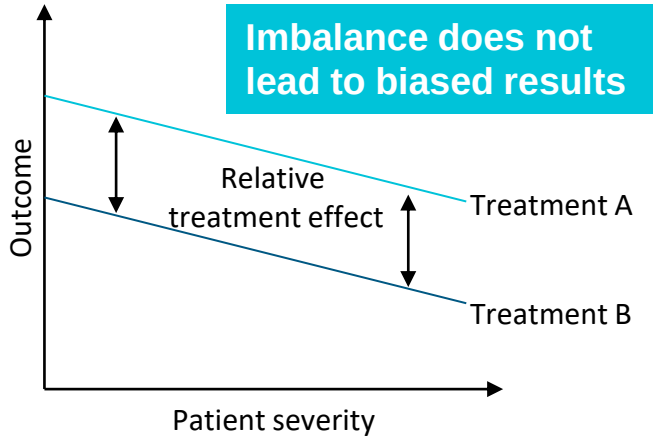
Treatment effect modifier vs prognostic variable

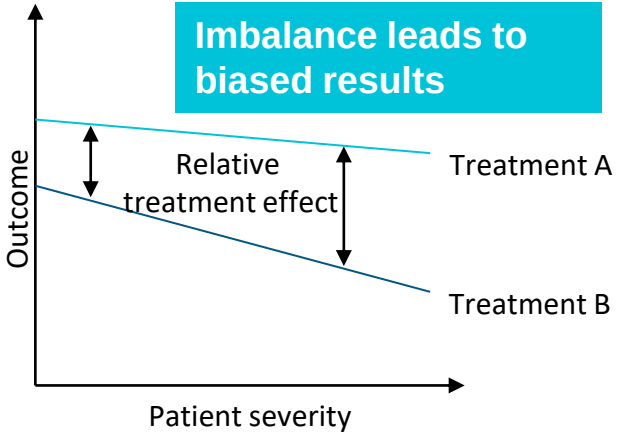
PV

Impacts a clinical outcome irrespective of treatment.
Impacts absolute effects, but not the relative effect.

TEM

Alters the effect of a treatment on a clinical outcome.
Impacts relative effects.





Jansen et al., Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report
VALUE IN HEALTH 17 (2014) 157–173

Comparability of the Trials: Key Inclusion Criteria

SPARTAN

Eligibility
- nmCRPC
- PSADT ≤ 10 months
- ECOG PS = 0 or 1

On-Study Requirement
- Continuous ADT

PROSPER

Eligibility
- nmCRPC
- PSADT ≤ 10 months
- ECOG PS = 0 or 1

On-Study Requirement
- Continuous ADT

ECOG PS, Eastern Cooperative Oncology Group performance status; PSADT, PSA doubling time.

Comparability of the Trials: Baseline Characteristics

BASELINE CHARACTERISTICS		PROSPER N = 1401		SPARTAN N =1207
PSA doubling time (m)	med PSA doubling time	3.7	>	4.4
	% PSA doubling time <6m	77		70
Age	med Age (years)	73.7	≈	74
	% Age < 75	54		52
med (Serum) PSA at baseline		10.8	>	7.8
% ECOG=1		19	<	23
% use of bone targeting agent		11	>	10
Total Gleason score at diagnosis	% Total Gleason score 2-4	2	≈	2
	% Total Gleason score 5-7	54		55
	% Total Gleason score 8-10	44		44
% Surgical prostate cancer procedures		54	<	57

How to compare treatments from different trials?

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		Individual patient level data (IPD)	**Summary data (AD)**
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PS: propensity score; ITC: indirect treatment comparison; NMA: network meta-analysis; MAIC: matching adjusted indirect; comparison; STC: simulated treatment comparison; ML-NMR: multilevel network meta-regression

MAIC: matching-adjusted indirect comparison

- Signorovitch et al., 2012
  - To balance the populations of an indirect comparison

    ⇒ Still comparing relative treatment effects

    ANCHORED MAIC

  - Can also be used to balance the populations in case of single arm trials or no common comparator in multi-arm trials

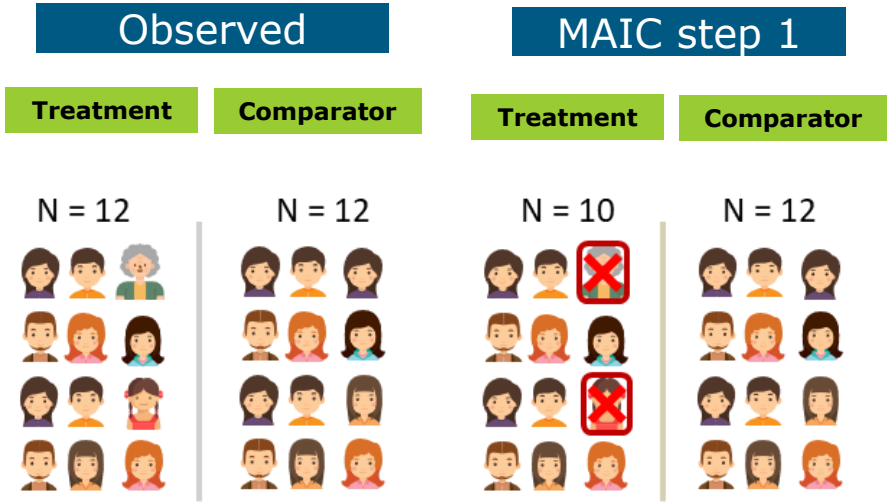
    ⇒ Comparing absolute treatment effects

    ⇒ Use of relative effect measures or validation of matching are not possible!

    UNANCHORED MAIC

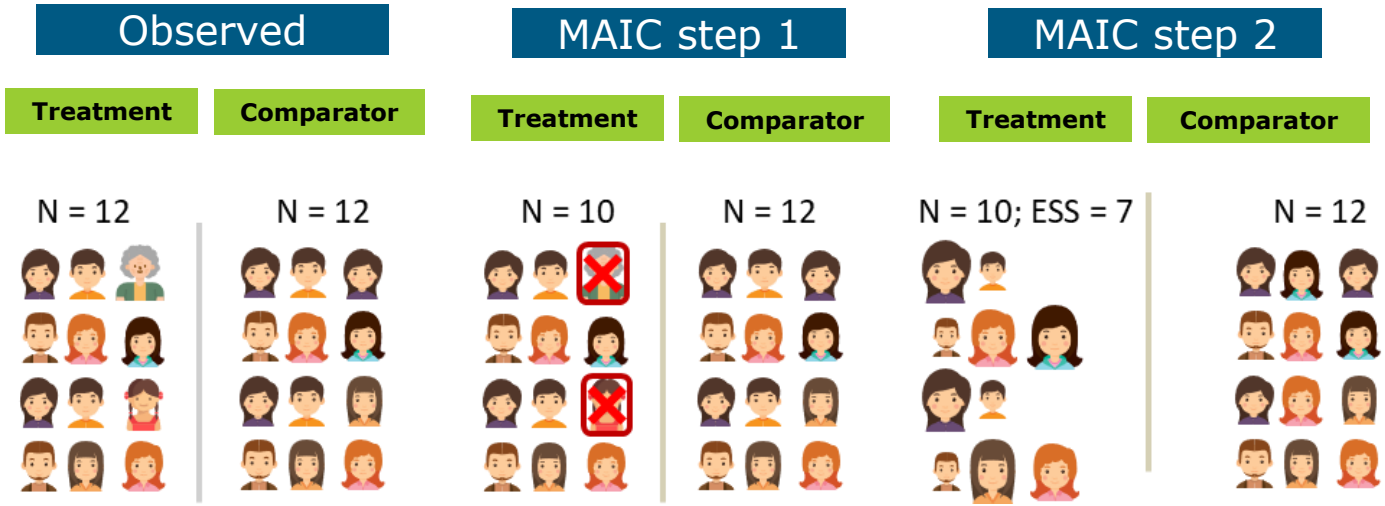
MAIC: step 1

- Exclude patients from IPD data that where also excluded from AD trial



MAIC: step 2

- Re-weight patients in IPD data (= pseudo population)
  - Match baseline characteristics to those reported in trials with AD data
  - ⇒ Balances trial populations
  - ⇒ How the treatment would perform in the comparator's population



MAIC: step 2

Weights = Inverse of odds of having enrolled in the IPD trial vs having enrolled in the comparator

= Propensity score weighting

Effective sample size (ESS or Neff) = Measure of impact of re-weighting on the available statistical information in de IPD

≈ Number of independent non-weighted patients that would be required to give an estimate with the same precision as the weighted sample

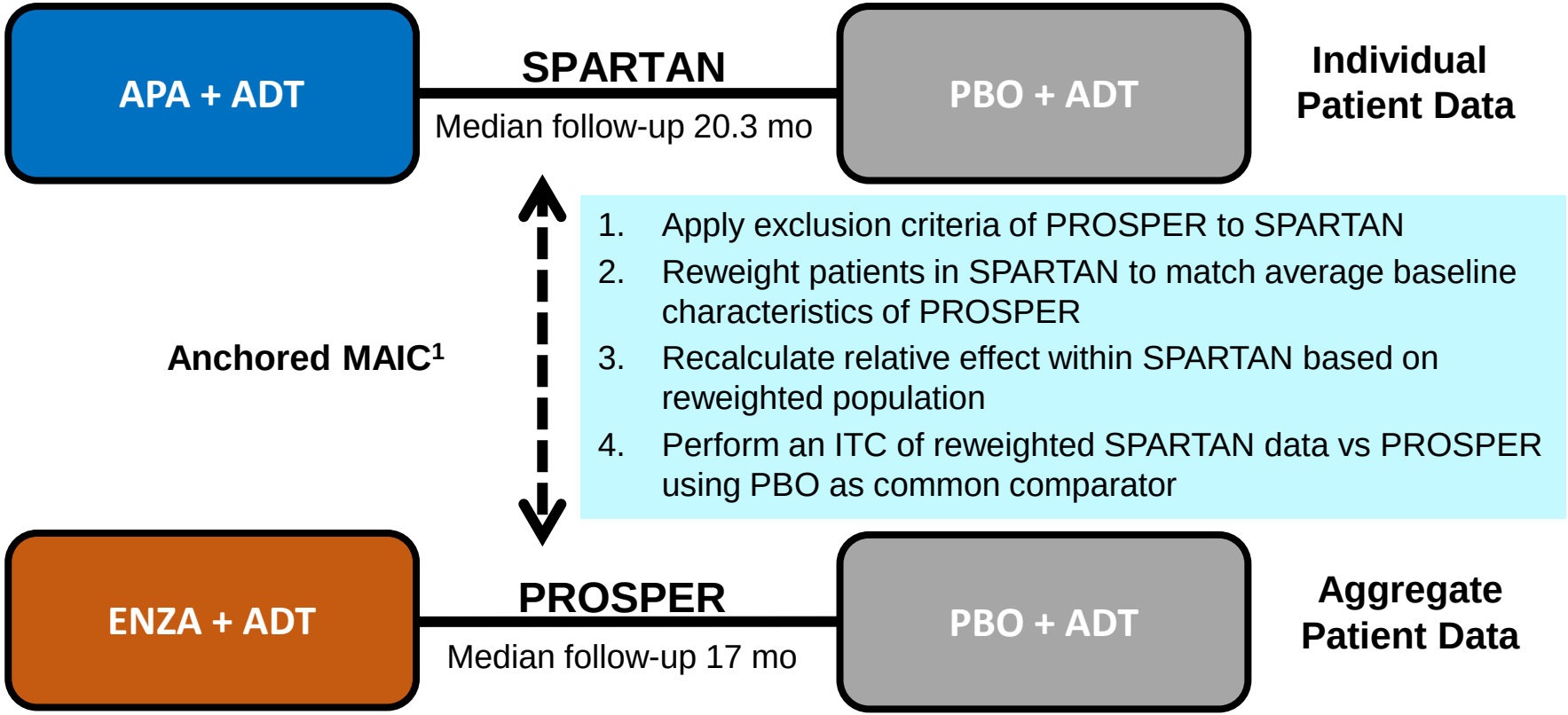
MAIC: step 3

- Compare relative treatment effect of the pseudo or weighted population with that of the published trial

Limitations of MAIC

- Can only compare two treatment at a time
- The relative treatment effect obtained is only valid in the population of the comparator
- Depends heavily on the available evidence in publications
  - E.g. If information about a characteristic is not reported, or a different scale/scoring system is used, we cannot match on it
- Depends on the ability to match with the publication
  - E.g. If the populations are too different, matching will be impossible or will lead to high uncertainty (very small N_{eff}) in the final comparison

Case study: methods



1. Signorovitch JE, et al. *Pharmacoeconomics*. 2010;28:935-945.

ITC After Matching

- Bucher ITC or frequentist NMA lack statistical power (standard error of the indirect comparison estimate is based on the simple addition of the two variances from the original studies)
- Major advantage of Bayesian approach: Answers a question directly relevant to health care decision-makers[1]

> *"Given the available evidence, how likely is it that one treatment is more beneficial than the other?"* [1]

- Therefore, we compare the HR/OR/DIFF based on the reweighted SPARTAN population with the reported HR/OR/DIFF from PROSPER in a Bayesian framework (Non-informative priors)

1. Jansen JP, et al. *Value Health*. 2011;14:417-428.

Outcomes of Interest

Efficacy end points (time to event, HR)

- Metastasis-free survival (MFS; primary end point)
- Overall survival (OS)

Tolerability end points (binary events, OR)

- Any adverse events (AEs)
- Any serious AEs (SAEs)
- ...

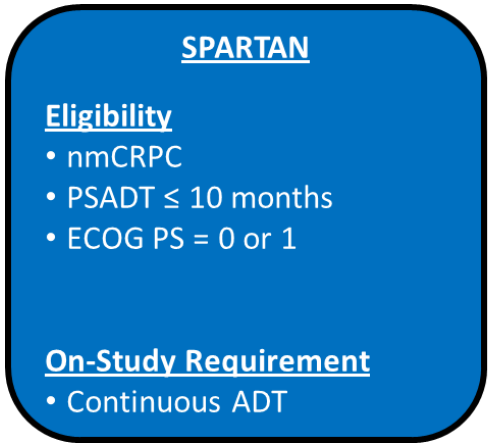
Health-related quality of life (continuous, DIFF)

- FACT-P

HR: hazard ratio; OR: odds ratio; DIFF: difference.

MAIC: step 1

- Exclude patients from IPD data that where also excluded from AD trial



- No patients need to be excluded!

ECOG PS, Eastern Cooperative Oncology Group performance status; PSADT, PSA doubling time.

MAIC: step 2

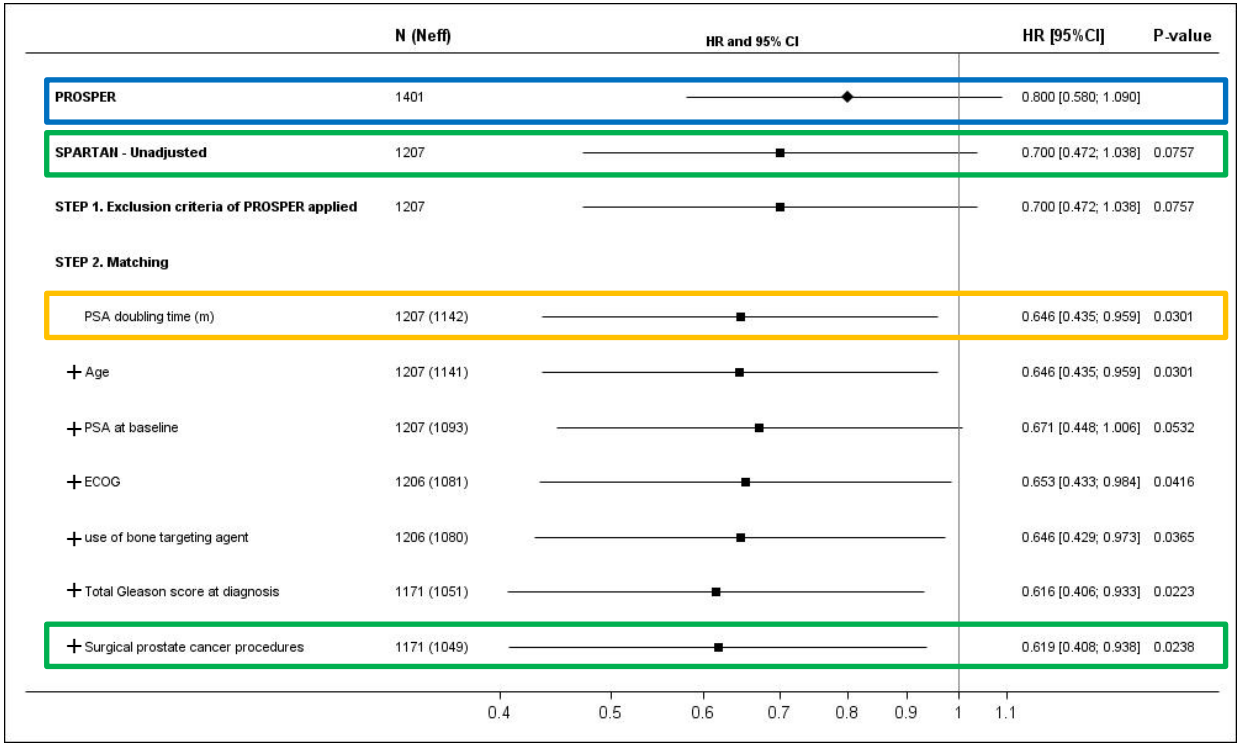
BASELINE CHARACTERISTICS		PROSPER N = 1401	SPARTAN N =1207	SPARTAN matched N =1171 Neff =1049
PSA doubling time (m)	med PSA doubling time	**3.7**	4.4	**3.7**
	% PSA doubling time <6m	**77**	70	**77**
Age	med Age (years)	**73.7**	74	**74**
	% Age < 75	**54**	52	**54**
med (Serum) PSA at baseline		**10.8**	7.8	**10.8**
% ECOG=1		**19**	23	**19**
% use of bone targeting agent		**11**	10	**11**
Total Gleason score at diagnosis	% Total Gleason score 2-4	**2**	2	**2**
	% Total Gleason score 5-7	**54**	55	**54**
	% Total Gleason score 8-10	**44**	44	**44**
% Surgical prostate cancer procedures		**54**	57	**54**

N_{eff}, effective sample size.

Within Trial Efficacy Results Before and After Matching
(HR, 95% CI)

	PROSPER	SPARTAN	
		Original N=1,207	MAIC-weighted N=1,171
Metastasis-Free Survival	0.290 [0.240; 0.350]	0.27 [0.22; 0.33]	0.26 [0.21; 0.33]
Overall Survival	0.800 [0.580; 1.090]	0.70 [0.47; 1.04]	0.62 [0.41; 0.94]

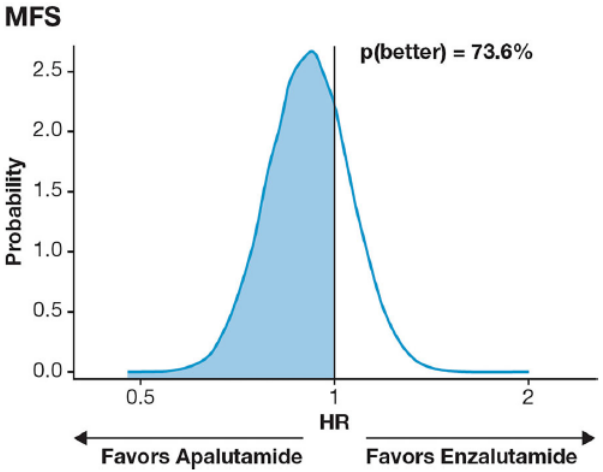
Within Trial OS Results Before and After Matching (HR, 95% CI)

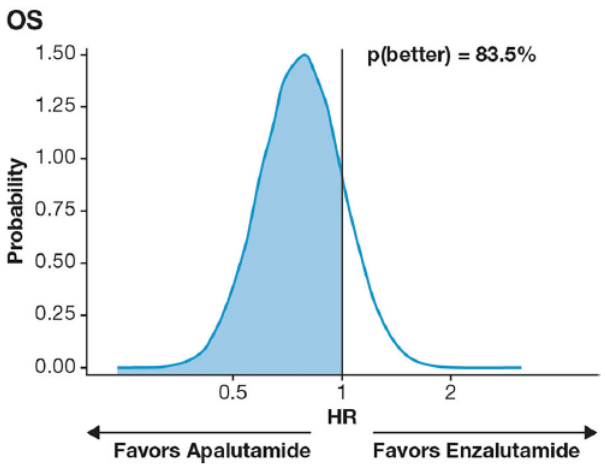


APA + ADT Compared With ENZA + ADT After Matching

Efficacy end points

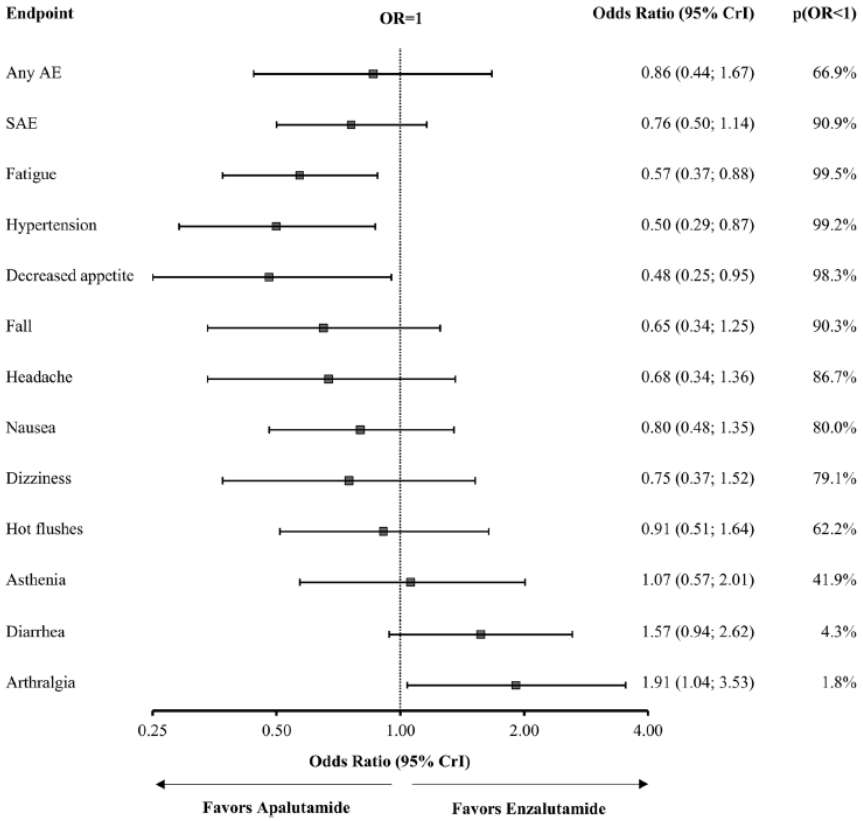
Apalutamide vs. enzalutamide	Unadjusted		MAIC-weighted	
	HR [95% CrI]	P(HR<1)	HR [95% CrI]	P(HR<1)
Metastasis-Free Survival	0.92 [0.69; 1.22]	72.8%	0.91 [0.68; 1.22]	73.6%
Overall Survival	0.88 [0.53; 1.45]	69.9%	0.77 [0.46; 1.30]	83.5%



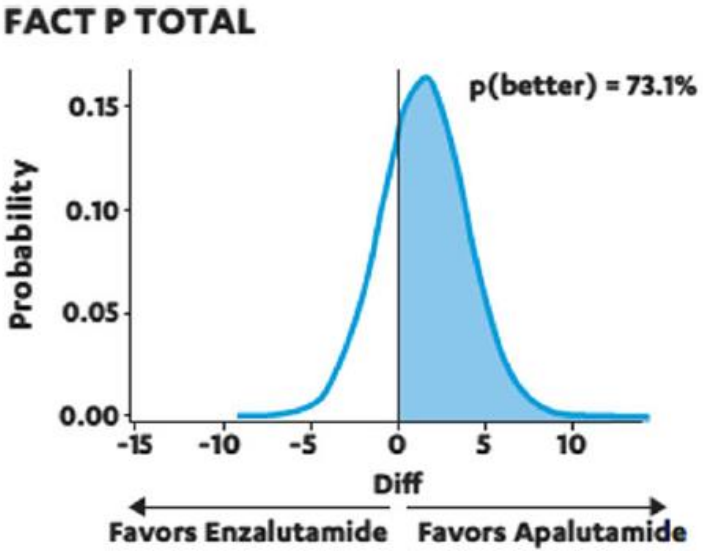


APA + ADT Compared With ENZA + ADT After Matching

Tolerability end points



Health-related quality of life



Limitations of the Analysis

- Matching could only be performed with characteristics reported in the PROSPER trial
- Although most clinically important baseline characteristics which may bias ITC results through effect modification were adjusted, residual bias could still exist due to unmeasured treatment effect modification

Discussion & Conclusions (results)

- MAIC results suggest that patients with nmCRPC treated with APA + ADT vs ENZA + ADT had
  - More favorable MFS and OS[1]
  - Better tolerability profile (less fatigue, hypertension,…)[2]
  - Improved HRQoL[2]

1. Chowdhury et al. *Adv Ther.* 2020 Jan;37(1):501-511.
2. Chowdhury et al. *Adv Ther.* 2020 Jan;37(1):512-526.

Discussion & Conclusions (methods)

- ITC (Bucher, NMA) generate unbiased estimates if no differences exists in patient characteristics that have an interaction with treatment (TEM)
- Matching had in impact on the ITC for OS but not for MFS
  - “PSA doubling time” is a TEM for OS
  - ITC without matching underestimated the treatment benefit of APA vs ENZA for OS
- While Frequentist statistic generally lack power to obtain stat. sign. results in an ITC, the Bayesian framework offers the benefit of answering the questions “How likely is it that, provided the available evidence, one treatment is more beneficial that the other.

Thank you!

Questions?