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ORIGINAL RESEARCH

Matching-adjusted indirect treatment comparison of the efficacy of enzalutamide versus apalutamide for the treatment of nonmetastatic castration-resistant prostate cancer

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Background: To date, the efficacy of the androgen receptor inhibitors enzalutamide and apalutamide for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC) has not been compared directly in a clinical trial setting. Indirect comparisons can be used to assess relative efficacy and provide important information to guide treatment decisions. PROSPER and SPARTAN were double-blind, randomized, placebo-controlled, phase III trials in patients with nmCRPC with overall similar study designs and inclusion and exclusion criteria. Using an anchored matching-adjusted indirect comparison, based on the final data from the PROSPER and SPARTAN studies, we assessed the comparative efficacy of enzalutamide and apalutamide, both plus androgen deprivation therapy.

Methods: Using placebo as the common comparator, individual patient data from PROSPER were matched to the aggregate patient data from SPARTAN and efficacy endpoints from PROSPER were re-weighted accordingly. Patient baseline characteristics and endpoints were clinically and statistically tested to identify potential effect modifiers, according to National Institute for Health and Care Excellence guidelines. Hazard ratios for overall survival (OS), metastasis-free survival (MFS), and time to chemotherapy (TTCx) were re-estimated for PROSPER using weighted Cox proportional hazards models and indirectly compared with those of SPARTAN using a Bayesian network meta-analysis.

Results: Estimated hazard ratios [95% credible interval (CrI)] for enzalutamide versus apalutamide were 0.80 (95% CrI 0.58-1.10) for OS, 0.94 (95% CrI 0.69-1.29) for MFS2, and 0.90 (95% CrI 0.63-1.29) for TTCx. Similar results were seen for sensitivity analyses conducted for OS and MFS. Bayesian probability analyses showed a 91.7% favoring enzalutamide for OS, 65.1% for MFS, and 71.4% for TTCx.

Conclusions: The results of this matching-adjusted indirect comparison of final data from PROSPER and SPARTAN indicate comparable efficacy of enzalutamide and apalutamide with potentially a greater probability of longer MFS, OS, and TTCx in patients with nmCRPC treated with enzalutamide versus apalutamide.

Key words: apalutamide, effect modifiers, enzalutamide, network meta-analysis, nonmetastatic castration-resistant prostate cancer, matching-adjusted indirect comparison

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men worldwide.[1] Androgen deprivation therapy (ADT) has been the mainstay of treatment of prostate cancer for many years and is used in combination with radiotherapy for intermediate- and high-risk localized disease as well as for metastatic hormone-sensitive prostate cancer.[2] Most men develop resistance to ADT, however, leading to castration-resistant prostate cancer (CRPC) and eventually metastatic CRPC,[3-6] the development of which is associated with a poor prognosis.[7-9] The efficacy of the androgen receptor inhibitors enzalutamide and apalutamide for the endpoint of metastasis-free survival (MFS) was assessed in the phase III studies PROSPER (NCT02003924) and SPARTAN (NCT01946204), respectively,[10-13] leading to their approval for use in patients with nonmetastatic CRPC (nmCRPC) and a short prostate-specific antigen (PSA) doubling time.

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The efficacy and safety of enzalutamide and apalutamide have not been directly compared in a clinical trial; in such situations, indirect treatment comparisons (ITCs) can indicate relative efficacy and safety. The gold standard technique for ITCs is a network meta-analysis (NMA); however, these can be subject to bias if there are known sources or uncertainty of heterogeneity between clinical trials, such as different endpoint definitions or potential imbalances in effect modifiers. A matching-adjusted indirect comparison (MAIC) is an approved method of ITC that allows adjustment for effect modifiers that may differ across trials and that affect relative efficacy.[14,15] MAICs can be anchored, with a common comparator arm in each trial, or unanchored, such as for single-arm studies.[14,15] Effect modifiers should be formally tested, clinically and statically, using National Institute for Health and Care Excellence (NICE) guidelines.[14] Matching of baseline characteristics is carried out using individual patient data (IPD) from an index trial and summary data from another trial. Efficacy endpoints are re-weighted in the index trial to mimic the comparator population for which only published data are available; the weighting process reduces the effective sample size (ESS), which is the number of independent non-weighted individuals required to produce estimates with the same level of precision as the weighted sample.[14] Adjusted hazard ratios (HRs) based on the matched population are then compared with the HRs in the comparator trial.

Several ITCs, both NMA and MAIC, involving enzalutamide and apalutamide have been published previously and have shown comparable efficacy between enzalutamide and apalutamide.[16-23] A recent MAIC of the efficacy data from the PROSPER and SPARTAN studies, using the first interim analysis clinical data from the primary PROSPER and SPARTAN publications,[10,12] suggested that apalutamide has a higher probability of more favorable overall survival (OS) and MFS versus enzalutamide.[17] Since then, final data from PROSPER and SPARTAN studies have been published.[11,13]

The publication of final data from the PROSPER and SPARTAN studies offers an opportunity to carry out an MAIC with more extensive follow-up data and may support the robustness of previous ITC results. Therefore, the objective of this analysis is to assess the comparative efficacy of enzalutamide and apalutamide by means of an MAIC, according to published guidelines,[14,15] based on the final data from the PROSPER and SPARTAN studies.[11,13]

METHODS

Summary of PROSPER and SPARTAN studies

PROSPER and SPARTAN were both double-blind, randomized, placebo-controlled, phase III trials with similar study designs and inclusion and exclusion criteria. PROSPER enrolled 1401 patients (933 randomized to enzalutamide; 468 to placebo) and SPARTAN enrolled 1207 patients (806 randomized to apalutamide; 401 to placebo).[10,12] Key inclusion criteria for PROSPER were a diagnosis of nmCRPC with disease progression despite treatment with ADT, based on a baseline PSA level of $\geq$2 ng/ml, a minimum of three rising PSA values at weekly intervals or longer, and a PSA doubling time of $\leq$10 months. Patients with soft-tissue pelvic disease could be included in cases where the short axis of the largest malignant lymph node was $<$1.5 cm.[10] Patients eligible for inclusion in the SPARTAN trial also had nonmetastatic castration-resistant adenocarcinoma of the prostate with a PSA doubling time of $\leq$10 months, while receiving continuous ADT. In addition, eligible patients had no local or regional nodal disease or had malignant pelvic lymph nodes that measured $<$2 cm in the short axis.[12] Among the 1401 patients from PROSPER, 14.6% were from North America, 49.3% from Europe, and 36.2% from the rest of the world.[10,13] Among the 1207 patients from SPARTAN, 34.7% were from North America, 49.6% from Europe, and 15.7% from the rest of the world.[24]

Both PROSPER and SPARTAN studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation for Good Clinical Practice, and local regulations. The study protocols were approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients. Informed consent for the MAIC was not required given the de-identified nature of the PROSPER IPD and the use of anonymized, previously published data from SPARTAN.[11,12,25]

Outcome measures

Outcome measures considered for the MAIC analyses were MFS, OS, and time to chemotherapy (TTCx). MFS was defined as the time from randomization to radiographic progression at any time or death up to 112 days after treatment discontinuation without radiographic progression, whichever occurred first, in PROSPER[10]; and, as the time from randomization to the first detection of distant metastasis on imaging, or death, in SPARTAN.[12] The PROSPER definition of MFS was similar to the SPARTAN progression-free survival (PFS) definition of time from randomization to the first detection of local or distant metastatic disease on imaging, as assessed by means of blinded independent central review, or death due to any cause, whichever occurred first.[12] Therefore, the PROSPER MFS definition was adjusted (MFS2), with a modified censoring rule by which any death (including those that occurred $>$112 days after treatment discontinuation) was considered as progression, and compared with PFS in SPARTAN as base case for MFS comparison.

Selection of baseline characteristics

Selection of the disease and patient baseline characteristics used for the matching was based on their potential influence on the relative efficacy of MFS, OS, and TTCx. In accordance with the NICE Decision Support Unit (NICE DSU) recommendations, the choice of matching parameters was justified by clinical expert advice and empirical identification of all effect modifiers.[14] A thorough statistical assessment of effect modification was conducted separately for each outcome measure (Supplementary Table S1, available

at https://doi.org/10.1016/j.esmoop.2022.100510). A Cox proportional hazards model combined with stratified analysis and a likelihood ratio test (significance threshold 0.2) was used to determine the effect modifiers to be included in the MAIC. Only variables found to be effect modifiers were included in the matching; prognostic factors that were not effect modifiers were excluded. Region, Eastern Cooperative Oncology Group performance status (ECOG PS) score, and previous prostate cancer treatment were included as effect modifiers for OS, MFS, and TTCx. In addition, patient age and use of bone-sparing/targeting agent were included as effect modifiers for both MFS and OS. PSA doubling time and PSA at study entry for both OS and TTCx, and effect modifiers specific to MFS, were race and surgical prostate cancer procedures.

Baseline disease and patient characteristics between the PROSPER and SPARTAN studies were similar for the majority of variables (Table 1); variables that differed between the PROSPER and SPARTAN studies were baseline PSA, ECOG PS score, and region.[11,13]

Matching trial populations

As PROSPER and SPARTAN dosing regimens were comparable, the placebo treatment is the common comparator in this anchored MAIC. Intent-to-treat populations were used from both studies; however, IPD from PROSPER were re-weighted to match the selected baseline characteristics of the SPARTAN trial, for which only aggregate results were available.[25] The matching process reduced the ESS of the selected PROSPER population (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100510).[14] In line with NICE DSU recommendations, weightings for each patient were computed using the quasi-Newton optimization method, i.e. the Broyden—Fletcher—Goldfarb—Shanno algorithm.[14]

Statistical analyses

The matching optimization algorithms and analyses were implemented in R version 3.5.1 (the R Foundation for statistical computing, Vienna, Austria) and OpenBUGS version 3.2 (MRC Biostatistics Unit, Cambridge, UK). Cox proportional hazards models fitted to the weighted data were used to estimate HRs for enzalutamide versus placebo; the re-weighted HRs were then compared with the published HRs for apalutamide versus placebo[9,11] using a Bayesian NMA to estimate posterior median HRs [95% credible interval (CrI)] for enzalutamide versus apalutamide. Bayesian posterior distributions of the HRs for enzalutamide versus apalutamide were visually presented for base-case analyses. A graphical representation of MFS and OS was utilized to identify differences and similarities between our data and those of previous ITCs.

Sensitivity analyses

To assess the robustness of results, several sensitivity analyses were carried out. A sensitivity analysis was carried out using the primary definitions of MFS from PROSPER and SPARTAN.[10,12] To account for patient crossover in PROSPER from placebo to enzalutamide and/or other therapies, a sensitivity analysis was carried out on OS adjusted for treatment switching using a rank-preserving structural failure time model (RPSFTM) which was compared with crossover adjusted OS in SPARTAN. To assess the impact of region on MFS and OS, sensitivity analyses were carried out excluding region as an effect modifier. Of the prior treatments, prostatectomy or radiation therapy, gonadotropin-releasing hormone analogue agonist, and first-generation antiandrogen therapy, the likelihood ratio test only identified first-generation antiandrogen therapy as a potential effect modifier. As such, a sensitivity analysis was carried out for OS with no matching for prior first-generation antiandrogen therapy. A final sensitivity analysis was carried out for OS using an identical set of patient baseline characteristics used for a previously published MAIC of the first interim analysis.[17]

RESULTS

Patient baseline characteristics

Baseline characteristics (base case) were balanced after matching the IPD from PROSPER to the aggregate-level data from SPARTAN for MFS2, OS, and TTCx (Table 1). As a result of the matching process, the sample size of the selected PROSPER population was reduced to an ESS equal to 858 patients for OS, 811 for MFS2, and 873 for TTCx (Table 2), where region had the largest effect on the reduction of the sample size (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100510).

MAIC results

MFS2. The re-weighted HR for enzalutamide versus placebo for MFS2 was numerically lower than the unweighted HR calculated before matching, 0.27 [95% confidence interval (CI) 0.22-0.35] and 0.31 (95% CI 0.26-0.37), respectively (Table 2). In the base-case analysis where the re-weighted MFS2 HR was compared with the PFS HR for apalutamide versus placebo from SPARTAN,[12] the estimated HR for enzalutamide versus apalutamide was 0.94 (95% CrI 0.69-1.29; Table 2). The posterior distribution of the HR of enzalutamide versus apalutamide for MFS2 showed a 65.1% probability that MFS was longer with enzalutamide versus apalutamide (Figure 1A).

Similarly, comparable efficacies between enzalutamide and apalutamide were seen in the sensitivity analysis using the primary definition of MFS from both PROSPER and SPARTAN studies, estimated HR 0.97 [95% CrI 0.70-1.34; $P(HR < 1)$ 58.4%, data not shown]. When region was excluded, MAIC results suggested a slightly more favorable benefit for enzalutamide [HR 0.91 (95% CrI 0.68-1.21)] with a 75.7% probability that MFS was longer with enzalutamide versus apalutamide (data not shown).

OS. After re-weighting the PROSPER population to be similar with the SPARTAN population, the MAIC-adjusted OS HR for enzalutamide versus placebo was 0.62 (95% CI 0.49-

Table 1. Patient baseline characteristics before and after matching

Effect modifier[a]	MFS		OS		TTCx		SPARTAN[11] $n = 1207$
	PROSPER (pre-match) $n = 1399$	PROSPER (post-match) $n = 811$	PROSPER (pre-match) $n = 1395$	PROSPER (post-match) $n = 858$	PROSPER (pre-match) $n = 1395$	PROSPER (post-match) $n = 873$	
Age, median, years	74	74	74	74	—	—	74
Region, %							
Europe	49.3	49.6	49.3	49.6	49.3	49.6	49.6
North America	14.6	34.7	14.6	34.7	14.6	34.7	34.7
Rest of the world	36.2	15.7	36.2	15.7	36.2	15.7	15.7
Race, %							
Asian	16.4	11.6	—	—	—	—	11.6
Black or African American	2.2	5.6	—	—	—	—	5.6
White	70.7	66.3	—	—	—	—	66.3
Other	10.7	16.5	—	—	—	—	16.5
ECOG PS 1, %	19.3	22.6	19.3	22.6	19.3	22.6	22.6
PSA doubling time <6 months, %	—	—	77	71.3	77	71.3	71.3
Use of bone-sparing/targeting agent, %	11	10	11	10	—	—	10
Previous prostate cancer treatment: first-generation antiandrogen agent, %	—	—	62.9	73.1	62.9	73.1	73.1
Previous prostate cancer treatment: prostatectomy or radiation therapy, %	57.1	76.6	—	—	—	—	76.6
PSA at study entry, median	—	—	10.8	7.8	10.8	7.8	7.8
Surgical prostate cancer procedures, %	54	57	—	—	—	—	57

ECOG PS, Eastern Cooperative Oncology Group performance status; MFS, metastasis-free survival; NICE DSU, National Institute for Health and Care Excellence Decision Support Unit; OS, overall survival; PSA, prostate-specific antigen; TTCx, time to chemotherapy.
[a]Identified according to NICE DSU guidelines.[16]

0.79), which was numerically lower than the unweighted HR reported in the trial, 0.73 (95% CI 0.61-0.88). In the base-case analysis, the MAIC results indicated an OS benefit for enzalutamide versus apalutamide [HR 0.80 (95% CrI 0.58-1.10); Table 2] with a 91.7% probability of longer survival with enzalutamide versus apalutamide (Figure 1B).

The indirect HR for enzalutamide versus apalutamide was 0.89 (95% CrI 0.65-1.21) for the OS RPSFTM-adjusted

Table 2. Anchored MAIC results for enzalutamide versus apalutamide

Analysis	PROSPER (enzalutamide versus placebo) unweighted HR (95% CI) *P* value ($n = 1401$)	PROSPER (enzalutamide versus placebo) MAIC weighted HR (95% CI) *P* value	PROSPER ESS after matching	SPARTAN (apalutamide versus placebo) HR (95% CI) *P* value	MAIC result (enzalutamide versus apalutamide) HR (95% CrI)
MFS2	0.31 (0.26-0.37) $P < 0.001$	0.27 (0.22-0.35) $P < 0.001$	811	0.29 (0.24-0.36) $P < 0.001$	0.94 (0.69-1.29)
MFS using primary MFS definitions	0.30 (0.25-0.36) $P < 0.001$	0.27 (0.21-0.35) $P < 0.001$	811	0.28 (0.23-0.35) $P < 0.001$	0.97 (0.70-1.34)
MFS2 excluding region as an effect modifier	0.31 (0.26-0.37) $P < 0.001$	0.26 (0.22-0.32) $P < 0.001$	1238	0.29 (0.24-0.36) $P < 0.001$	0.91 (0.68-1.21)
OS (base case)	0.73 (0.61-0.88) $P = 0.001$	0.62 (0.49-0.79) $P < 0.001$	858	0.78 (0.64-0.96) $P = 0.016$	0.80 (0.58-1.10)
OS (adjusted for treatment switching by RPSFTM)	0.72 (0.60-0.87) $P < 0.001$	0.61 (0.48-0.78) $P < 0.001$	858	0.69 (0.56-0.84) $P = 0.0002$	0.89 (0.65-1.21)
OS excluding region as an effect modifier	0.73 (0.61-0.88) $P = 0.001$	0.72 (0.59-0.88) $P = 0.00126$	1226	0.78 (0.64-0.96) $P = 0.016$	0.92 (0.69-1.23)
OS (no matching of prior therapy[a])	0.73 (0.61-0.88) $P = 0.001$	0.66 (0.52-0.83) $P < 0.001$	918	0.78 (0.64-0.96) $P = 0.016$	0.84 (0.62-1.14)
OS (using Chowdhury et al.[17] matching variables[b])	0.73 (0.60-0.88) $P = 0.001$	0.76 (0.62-0.93) $P = 0.007$	1177	0.78 (0.64-0.96) $P = 0.016$	0.97 (0.72-1.30)
TTCx	0.55 (0.44-0.67) $P < 0.001$	0.57 (0.44-0.74) $P < 0.001$	873	0.63 (0.49-0.81) $P < 0.001$	0.90 (0.63-1.29)

CI, confidence interval; CrI, credible interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; MFS, metastatic-free survival; MFS2, adjusted metastatic-free survival; NMA, network meta-analysis; OS, overall survival; RPSFTM, rank-preserving structural failure time model; TTCx, time to chemotherapy.
[a]Treatment with first generation antiandrogen agent (Y/N).
[b]Compared with effect modifiers included in the base case, Chowdhury et al.[17] 'region' and 'prior therapy' were excluded from the matching and 'Gleason score' and 'surgical prostate cancer' were included.

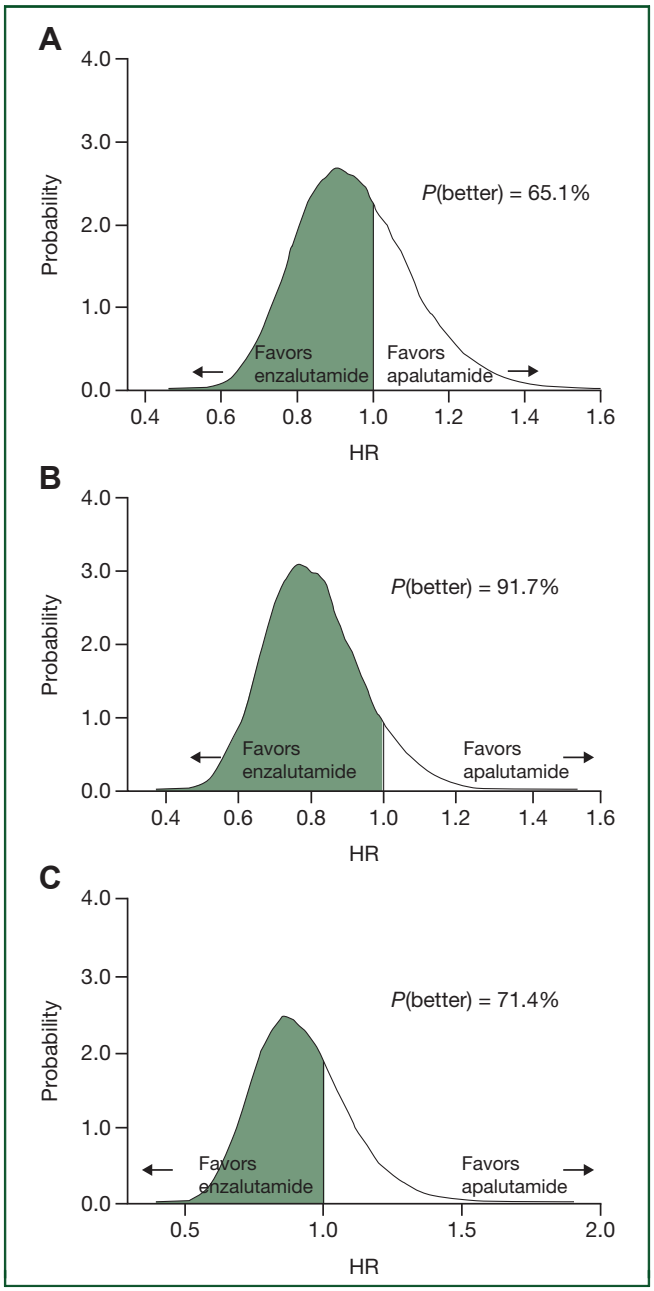

Figure 1. Posterior distribution of the HR (95% CrI) of enzalutamide versus apalutamide for (A) MFS2 (base case), (B) OS (base case), and (C) TTCx (base case).

CrI, credible interval; HR, hazard ratio; MFS, metastasis-free survival; MFS2, adjusted metastasis-free survival; OS, overall survival; TTCx, time to chemotherapy.

sensitivity analysis, 0.92 (95% CrI 0.69-1.23) for the sensitivity analysis excluding region as an effect modifier, 0.84 (95% CrI 0.62-1.14) for the sensitivity analysis with no matching for prior first-generation antiandrogen therapy, and 0.97 (95% CrI 0.72-1.30) for the sensitivity analysis using variables matched to the MAIC of the first interim analysis from PROSPER and SPARTAN studies.[17] The probability of an OS gain for enzalutamide was lower compared with baseline when excluding region (72.1%, data not shown). In all comparisons, the 95% CrI included 1.0, indicating comparable efficacy of enzalutamide and apalutamide (Table 2).

TTCx. The re-weighted HR for enzalutamide versus placebo for TTCx was numerically higher than the unweighted HR calculated before matching, 0.57 (95% CI 0.44-0.74) and 0.55 (95% CI 0.44-0.67), respectively (Table 2). The re-weighted TTCx HR was compared with the TTCx HR for apalutamide versus placebo from SPARTAN[11]; the estimated HR for enzalutamide versus apalutamide was 0.90 (95% CrI 0.63-1.29), indicating comparable efficacy of enzalutamide and apalutamide (Table 2), but with a 71.4% probability that TTCx is longer with enzalutamide versus apalutamide (Figure 1C).

Comparison of OS and MFS MAIC results and previous ITCs. Compared with previously published ITCs,[16-23] especially ITCs that utilized final PROSPER and SPARTAN data, the base-case MAIC results for MFS and OS for enzalutamide versus placebo and enzalutamide versus apalutamide (Figure 2) were similar, with overlapping CIs and CrIs for the indirect HR estimates.

DISCUSSION

In this study, we indirectly assessed the efficacy of enzalutamide and apalutamide in patients with nmCRPC using an MAIC that allows adjustment for differences across the PROSPER and SPARTAN trials that could affect relative efficacy. Our assessment, based on final data from PROSPER and SPARTAN and including several sensitivity analyses, showed comparable treatment effects in terms of MFS, OS, and TTCx, with CrIs for indirect HRs including 1.0 for all endpoints. Bayesian uncertainty analysis suggested higher probabilities of efficacy benefits for enzalutamide.

Enzalutamide and apalutamide have not been compared in randomized, controlled trials in patients with nmCRPC, but their relative efficacy can be assessed indirectly. NMA is the gold standard for ITC; however, results may be biased if there is considerable heterogeneity across comparative trials. The MAIC method uses IPD from one trial (the index trial, in our case PROSPER) and compares this to aggregated data from a comparator trial (SPARTAN) by adjusting for trial differences. The method is useful when endpoints are defined differently and when there are cross-trial differences in baseline characteristics that are known effect modifiers. MAIC is also helpful when there is uncertainty about potential effect modifiers and can therefore validate NMA results. In circumstances where effect modifiers are absent or play a minor role due to limited imbalances across trials, results between MAIC and NMA will be similar. MAIC is less useful when there is a lack of overlap between trials.

We found evidence of several effect modifiers, confirmed by both clinical and statistical review, but with some variation across endpoints. ECOG PS score, previous prostate cancer treatments, and geographic region were effect modifiers across all endpoints, whereas important prognostic factors like PSA doubling time (MFS), PSA at study entry (MFS), and Gleason score (MFS, OS, and TTCx) were not consistently found to be effect modifiers. An investigation of effect modifiers' impact on the ESS demonstrated that region had the greatest impact on ESS reduction;

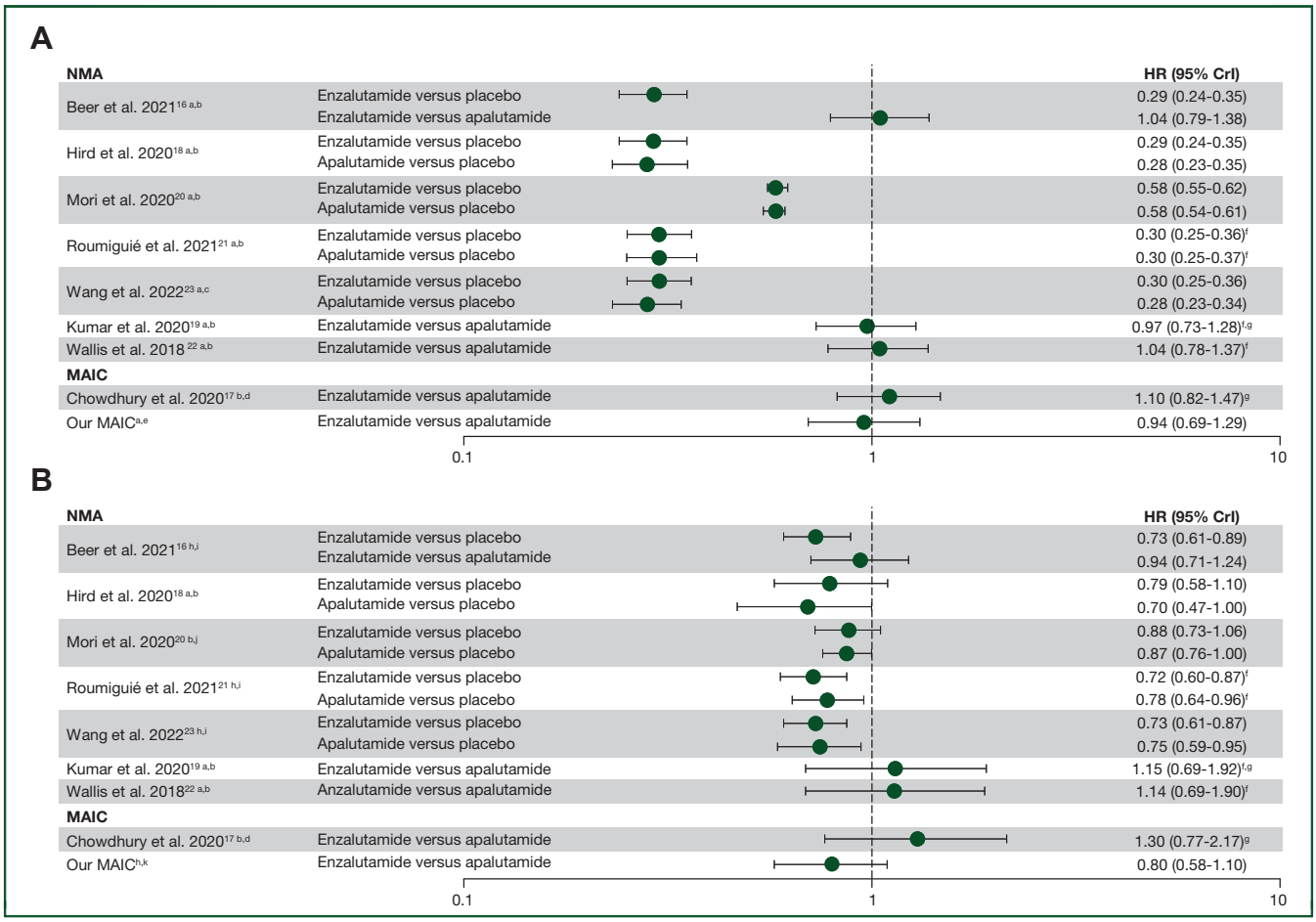

Figure 2. Forest plots of HR (95% CrI) for (A) MFS and (B) OS outcomes for this analysis and previously published ITCs.[16-23]

HRs between 0.1 and 1.0 favor the agent listed first in each comparison.

CI, confidence interval; CrI, credible interval; HR, hazard ratio; IA, interim analysis; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MFS, metastatic-free survival; NMA, network meta-analysis; OS, overall survival.

[a]ITC used published HR (95% CI) from SPARTAN IA1.

[b]ITC used published HR (95% CI) from PROSPER IA1.

[c]ITC used published MFS sensitivity analysis HR (95% CI), which included all deaths without evidence of radiographic progression, regardless of timing, from PROSPER IA1.

[d]HR (95% CI) for SPARTAN IA1 were weighted to match published PROSPER IA1 data.

[e]HR (95% CI) for PROSPER IA1 data were weighted to match published SPARTAN IA1 data.

[f]Meta-analysis of treatment effects measured HR (95% CI).

[g]HR (95% CI/95% CrI) displayed are inverted from the apalutamide versus enzalutamide values published.

[h]ITC used published HR (95% CI) from SPARTAN final analysis.

[i]ITC used published HR (95% CI) from PROSPER final analysis.

[j]ITC used published HR (95% CI) from SPARTAN IA2.

[k]HR (95% CI) for PROSPER final analysis data were weighted to match published SPARTAN final analysis data.

compared with SPARTAN, there were less North American patients (14.6% versus 34.7%), similar shares of European patients (~49%), and a higher share of patients outside these regions (36.2% versus 15.7%); adjusting for this difference reduced the ESS significantly. In general, however, the effect modifiers had a similar small impact on the ESS, with sample size reductions in our MAIC ranging from 61.3% to 65.6% of the original population size (including region) and 84.1% to 87.6% (excluding region), across the base-case and sensitivity analyses for OS, indicating good overlap as per the NICE DSU guidelines.[14]

Given similar trial designs, it was not surprising to find partly limited effects of MAIC adjustments on outcomes. In our base-case analysis of MFS, MAIC adjustment led to a minor numerical reduction in the HR for enzalutamide versus placebo from 0.31 (95% CI 0.26-0.37) to 0.27 (95% CI 0.22-0.35), and MAIC-adjusted HRs versus apalutamide equal to 0.94 (95% CrI 0.69-1.29). Region had a minor effect on MFS (HR 0.91; 95% CrI 0.68-1.21). MAIC adjustment, however, had a larger impact on OS where HRs for enzalutamide versus placebo in PROSPER equaled 0.73 (95% CI 0.61-0.88) and 0.62 (95% CI 0.49-0.79) before and after matching, respectively, with a resulting indirect treatment effect versus apalutamide that was numerically in favor of enzalutamide (HR 0.80; 95% CrI 0.58-1.10). Region contributed to a significant part of the adjustment; when region was excluded, the numerical difference was much smaller (HR 0.92; 95% CrI 0.69-1.23) with a reduced likelihood (from 91.7% to 72.1%) of a better OS. Adjusting for differences in use of prior first-generation antiandrogen

therapy did not change the results of comparability versus apalutamide.

In addition to the base-case analyses, several sensitivity analyses were conducted to determine the impact of endpoint definition. The primary efficacy endpoint MFS was not defined in the same way in PROSPER and SPARTAN; the PROSPER definition of MFS (time from randomization to radiographic progression, as determined by central review at any time, or as the time to death from any cause during the period from randomization to 112 days after the discontinuation of the trial regimen without evidence of radiographic progression, whichever occurred first) was more similar to the SPARTAN PFS definition (time from randomization to the first detection of local or distant metastatic disease on imaging, as assessed by means of blinded independent central review, or death due to any cause, whichever occurred first) which was used as our base case. When we used the primary definition of MFS across both trials, however, the results changed only marginally. Furthermore, there was significant crossover in both PROSPER and SPARTAN studies; however, using crossover corrected estimates did not change results of comparability between the treatments.

Standard NMAs typically assess uncertainty using a frequentist framework where the analysis either supports a difference between treatments or not.[22] This MAIC was based on Bayesian analysis which does not use a dichotomous approach, but rather assesses the likelihood that one treatment is better than the other. Base-case analysis suggested that there was a higher probability of a benefit for enzalutamide (91.7% for OS, 65.1% for MFS, and 71.4% for TTCx). The probabilities were dependent, however, on endpoint definitions and inclusion of effect modifiers. The importance of region as an effect modifier for the uncertainty assessment was evident in our analysis for OS. Excluding region, the probability that enzalutamide was more effective than apalutamide was reduced to 72.1% for OS and slightly changed for MFS (75.7%). The difference compared with our base-case analyses is reasonable; OS is usually affected by post-study treatments and the availability of these typically varies across regions and countries and may therefore affect results, whereas regional difference is less likely to affect MFS. We could only partly adjust for regional differences, as the classification of the remaining countries outside of North America and Europe was different, with PROSPER grouping all countries into the rest of the world, including Asia-Pacific, and SPARTAN only including Asia-Pacific countries. Results are therefore uncertain, but the inclusion of region seems important, at least for OS.

The results of our study are consistent with previous published ITCs which, despite variation in the datasets used [first interim analyses, second interim analysis of SPARTAN[26] (OS data) and final data from PROSPER and SPARTAN studies], have all shown comparable efficacy for enzalutamide and apalutamide.[16-23] Although numerical differences were seen between studies, explained by the applied method (NMA or MAIC) and the use of different data cuts, the estimated 95% CI and 95% CrI for the indirect HRs included 1.0 for both OS and MFS across all studies.

Chowdhury et al.[17] also compared enzalutamide and apalutamide using an MAIC and found comparable MFS and OS results, but with a higher likelihood for an OS (83.5%) and MFS (73.6%) benefit with apalutamide. Understanding the differences in these findings is of interest. First, our analysis used final OS data in PROSPER (HR 0.73) instead of the interim analysis (HR 0.80) to compare with SPARTAN (HR 0.78). Second, geographical region was not adjusted for in Chowdhury et al.[17]; it is unclear if this was an effect modifier in SPARTAN as no formal assessment of effect modifiers according to NICE guidelines were presented. Including the same baseline characteristics as in Chowdhury et al.,[17] but with final OS data, provided a 59.2% probability that enzalutamide had better OS efficacy. Furthermore, it is interesting to note that MAIC adjustment of other baseline characteristics had no effect on MFS in Chowdhury et al.,[17] consistent with our findings. Hence, although different IPD were used (Chowdhury et al.[17] used SPARTAN IPD to compare with published aggregated data from PROSPER, whereas this analysis used PROSPER IPD to compare with summary SPARTAN), updated OS data and inclusion of region likely explains the key difference between these findings.

A number of factors contribute to the strength of this study including: the methodology utilized in the MAIC, which was based on guidance from NICE DSU and the International Society for Pharmacoeconomics and Outcomes Research[14,15]; the clinical and statistical reviews carried out in accordance with the NICE DSU recommendations regarding the scientific rationale for effect modifier selection; the matching of IPD to published aggregate data; and the sensitivity analyses conducted. In addition, this comparison used the final data from the PROSPER and SPARTAN studies.[11,13]

Our study, however, has a few limitations. First, although the inclusion and exclusion criteria of SPARTAN and PROSPER studies were very similar, for patients enrolled in SPARTAN, malignant pelvic lymph nodes were required to measure <2 cm in the short axis, whereas this was restricted to <1.5 cm for PROSPER; this difference could be a source of potential bias in the results due to heterogeneity in the study design that cannot be adjusted for. Second, we did not have summary information on all potential variables in SPARTAN that could impact treatment effect; thus, residual bias due to unmeasured confounders may exist. Third, both crossover-adjusted and crossover-unadjusted versions of OS were explored; however, as OS was estimated in PROSPER using an RPSFTM and in SPARTAN using a naive censoring crossover approach,[25] it is uncertain how comparable the results are and subsequently the estimated HR should be interpreted with caution.

This analysis did not include an indirect comparison to darolutamide using the ARAMIS study as the duration of follow up for OS differed significantly (median of 17.9, 48, and 52 months for ARAMIS, PROSPER, and SPARTAN, respectively) and could not be adjusted for.[11,13,27]

Furthermore, our study did not include an assessment of safety, as a rigorous comparison was precluded by heterogeneity in adverse event (AE) reporting and variation in AE risks in the placebo arms of PROSPER and SPARTAN studies.[28] PROSPER reported AEs occurring in ≥10% of patients and SPARTAN publications reported AEs occurring in ≥15% of patients; the more restrictive threshold for AE reporting used in SPARTAN publications means that of 25 AE types reported across the trials, only 4 were mutually reported. Furthermore, absolute risks of AEs in the placebo arms differed considerably, making indirect comparisons across trials problematic.

Conclusion

This ITC confirmed the comparable efficacy profiles of enzalutamide and apalutamide in patients with nmCRPC described in previous publications of ITCs.[16-23] Given the similar trial designs for PROSPER and SPARTAN, the results of this MAIC using final OS data from the studies were consistent with our expectations of comparable efficacy of enzalutamide and apalutamide for the endpoints OS, MFS, and TTCx.

The Bayesian probability analyses were numerically in favor of enzalutamide being more effective than apalutamide, although these results should be treated with caution given differences in regional representation across the trials could not be fully adjusted for.[14]

Multiple clinical trials, including PROSPER and SPARTAN, have confirmed the importance of new hormonal therapies in the management of nmCRPC. There are several options available that are recommended for use in current treatment guidelines, including both enzalutamide and apalutamide.[2] The choice of treatment of nmCRPC should be driven by guidelines, patient needs, data from large randomized, controlled trials, local availability, and cost to patients. The results of this MAIC add further information for clinicians to use when selecting therapy for patients with nmCRPC and a rapid doubling time.

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DATA SHARING

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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