

Feasibility of indirect treatment comparisons between niraparib plus abiraterone acetate and other first-line poly ADP-ribose polymerase inhibitor treatment regimens for patients with *BRCA1/2* mutation-positive metastatic castration-resistant prostate cancer

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Supplementary Materials

1.1. Systematic literature review

Relevant studies were identified from Embase, MEDLINE[®] and MEDLINE[®] In-Process, Cochrane Database of Systematic Reviews, Cochrane Collaboration Central Register of Clinical Trials via Ovid.com, and ClinicalTrials.gov. The search focused on identifying peer-reviewed publications evaluating the efficacy, safety, health-related quality of life (HRQoL), and utilities/disutilities of first-line (1L) treatments for patients with *BRCA1/2* mutation-positive metastatic castration-resistant prostate cancer (mCRPC). A search of key conferences (not older than two years) and a hand-search of relevant SLRs and meta-analyses since January 2017 were also conducted. Exclusion criteria eliminated publications reporting on children, adults without mCRPC, adults with mCRPC who have not received prior endocrine manipulation, those that did not evaluate the treatment of interest, and those that did not report outcomes of interest (Table S1). Risk of bias was assessed using the Cochrane risk-of-bias 2.0 tool [1] for randomized controlled trials (RCT).

Table S1: Eligibility criteria used in the systematic literature review search strategy

	Inclusion criteria	Exclusion criteria
Population	1L population (men; aged ≥ 18 years) with mCRPC ^a and <i>BRCA</i> mutations (including those who may have been treated previously with NHT ^b , chemotherapy, ADT ^b , and first-generation anti-androgens ^c)	Publications reporting on patient populations in the following categories: • Children • Healthy volunteers • Patients with only non-cancerous prostate disease (such as benign prostatic hyperplasia) • Patients with malignancies other than prostate cancer • Patients with localised/locally advanced prostate cancer, biochemical recurrence, hormone-sensitive or non-metastatic prostate cancer (including non-mCRPC) • Patients with metastatic prostate cancer who have not received prior endocrine manipulation
Interventions	Anti-androgen: Apalutamide + AAP, AAP, enzalutamide, and darolutamide PARP inhibitor (monotherapy and combination therapy): Talazoparib, rucaparib, pamiparib, niraparib, olaparib + AAP, talazoparib + enzalutamide, pembrolizumab + olaparib, and olaparib + Xofigo [®] , fluzoparib) Corticosteroids: Prednisone/prednisolone	Publications that do not report data specific to treatments included in the inclusion criteria

Inclusion criteria		Exclusion criteria
	Radiopharmaceutical: Radium-223 (Xofigo®), Lu-PSMA-617 Chemotherapy: Docetaxel, cabazitaxel, and carboplatin Immunotherapy: Sipuleucel-T, durvalumab, tremelimumab, denosumab, nivolumab, pembrolizumab, ipilimumab, and DCVAC TK inhibitor: Masitinib AKT inhibitor: Ipatasertib Other non-PARP inhibitor combination therapy: Ipatasertib + Zytiga® + prednisone, isatuximab + cemiplimab, and Imfinzi + tremelimumab, cabozantinib + atezolizumab AR antagonist: Rezvilutamide	
Comparators	Best supportive care, placebo, other 1L treatments (as listed under interventions above)	NA
Outcomes	Efficacy PFS (radiographic PFS and other [clinical, biochemical, etc.]) PFS2 OS Time to symptomatic skeletal-related event or time to symptomatic progression or time to symptomatic progression (e.g., bone fracture or external beam radiation therapy) Time to PSA progression Time to pain progression Time to chronic opioid use Time to initiation of cytotoxic chemotherapy Safety Total patients with discontinuations Treatment discontinuation due to AEs Total all-cause AEs/SAEs Total treatment-related AEs/SAEs Individual AEs of interest: Priority ^d Hypertension Rash Cognitive/memory impairment Ischemic heart disease Fatigue Hepatotoxicity Fall Fracture Oedema	Publications that do not report any outcome of interest listed under inclusion criteria

	Inclusion criteria	Exclusion criteria
	Hypokalemia Arrhythmia Cardiac failure Others ^e Disturbance in attention Memory impairment Cognitive disorder Amnesia Asthenia Diarrhea Neutropenia (docetaxel) Febrile neutropenia (docetaxel) Thrombocytopenia (docetaxel) Anemia (docetaxel, PARPi) Chest pain/discomfort Hypothyroidism Dyspnea Nausea/vomiting Arthralgia PROs BPI-SF, FACT-P, and EQ-5D-5L	
Study design	The review will be limited to publications of studies with the following designs: RCTs (open-label extensions and post-hoc analyses) Single-arm interventional trials ^f	All publications exception RCTs and single-arm trials
Publication types	NA	Publications of the following types: Narrative publications Non-systematic reviews Case studies Case reports Editorials
Language restrictions	Only English language articles/conference abstracts will be included ^g	Journal articles and conference abstracts without English full text

Abbreviations: 1L, first line; AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; AE, adverse event; BPI-SF, Brief Pain Inventory-Short form; FACT-P, Functional Assessment of Cancer Therapy – Prostate; mCRPC, metastatic castration-resistant prostate cancer; NA, not applicable; NHT, new hormonal therapy; OS, overall survival; PARPi, poly ADP-ribose polymerase inhibitor; PFS, progression-free survival; PFS2, time to second progression on next line; PRO, patient-reported outcome; PSA, prostate-specific antigen; RCT, randomized controlled trial; SAE, serious adverse event; TKI, tyrosine kinase inhibitor

^a The mCRPC population was also described as being castrate-resistant, castration-resistant, hormone-resistant, and hormone-refractory

^b NHT and ADT were largely equivalent except that NHT was given in a neoadjuvant context. ADT was the mainstay treatment for prostate cancer and includes luteinizing hormone-releasing hormone agonists and antagonists such as leuporelin, goserelin, triptorelin, histrelin, buserelin, and degarelix.

^c Examples include bicalutamide, flutamide, and nilutamide.

^d Only priority individual AEs were planned for extraction.

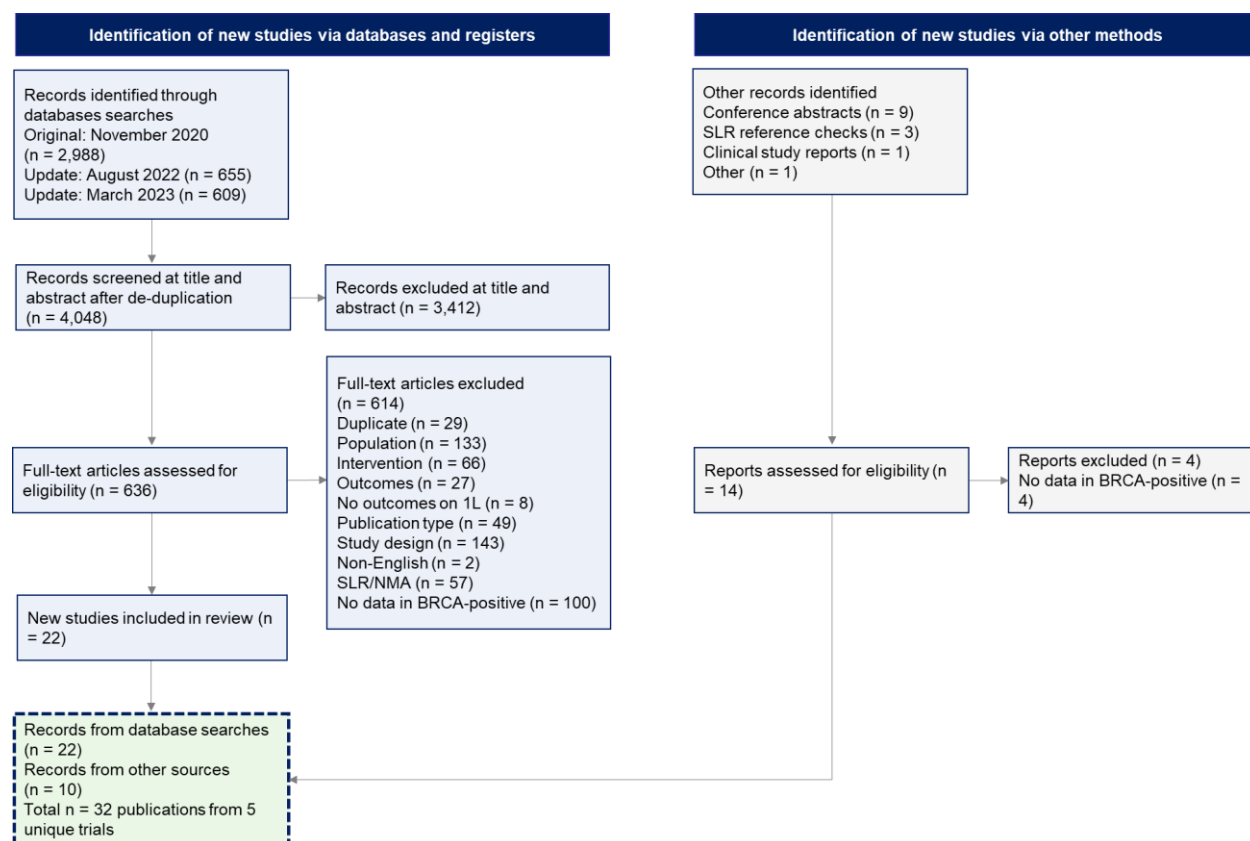
^e The availability of these outcomes was mapped across included studies, but the outcome data were not

extracted.

^f The single-arm interventional trials were limited only to apalutamide + AAP and niraparib + AAP.

^g Relevant non-English publications were listed under a separate exclusion code on the study listing for Janssen's reference. Of note, full texts were not retrieved for non-English publications; only English abstracts were screened to determine relevance.

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature flow diagram



Abbreviations: 1L, first line; NMA, network meta-analysis; SLR, systematic literature review

1.2.Comparability assessment

Table S2. Criteria used to assess appropriateness of NMA, anchored PAIC, or unanchored PAIC to facilitate ITCs between niraparib plus AAP and relevant comparators

Criteria	Rationale	Relevant for...		
		NMA	Anchored PAIC	Unanchored PAIC
Evidence structure				
Niraparib plus AAP is indirectly connected to relevant comparators in an evidence network	As long as a relevant comparator is connected to a network including niraparib plus AAP, NMA may be considered to facilitate an ITC between these treatments.	✓		
Relevant comparator compared with AAP in RCT	Pairwise anchored PAICs require a relevant comparator to be connected to niraparib plus AAP via AAP.		✓	
Data availability in BRCA-positive population				
Baseline characteristics	To assess (and if necessary, adjust for) differences in TEMs among the BRCA-positive patients informing the ITCs.	✓	✓	
Arm-level	If there are imbalances in PVs within an RCT, unanchored PAIC should adjust for differences only in the BRCA-positive patients informing the ITC.			✓
Sufficient outcome data	A RTE and corresponding standard error are required to inform the ITC in the BRCA-positive population.	✓	✓	
Arm-level	Only an absolute treatment effect and its corresponding standard error inform the ITC in the BRCA-positive population.			✓
Within-trial heterogeneity or bias				
Study characteristics				
Blinding	To assess potential for bias of trial-specific absolute treatment effects or RTEs due to deviations from assigned interventions [2]	✓	✓	✓
Concealment of randomization	To assess potential for bias of trial-specific RTEs due to selection enrolment [2]	✓	✓	
Patients randomized within BRCA-positive population (e.g., through restriction criteria or stratified randomization)	To assess potential for bias of trial-specific RTEs due to imbalances of PVs between arms within a trial [3]	✓	✓	
Data maturity	Trial-specific RTEs reported at interim analyses may not reflect RTE at planned final analyses [4].	✓	✓	✓

Criteria	Rationale	Relevant for...		
		NMA	Anchored PAIC	Unanchored PAIC
Treatment crossover	Permitting patients to crossover from control arm to experimental arm after progression will bias unadjusted trial-specific RTEs in favor of control arm for longer-term outcomes (e.g., OS)	✓	✓	
Sample size	Treatments effects may be susceptible to random error due to small sample size and number of events.	✓	✓	✓
Between-trial heterogeneity				
<i>Study characteristics</i>				
Median follow-up	If the trial-specific RTEs vary over time, then the RTEs should be synthesized at the same time. Unanchored PAICs should only be conducted at a similar median follow-up time.	✓	✓	✓
Location	Standard of care may vary across regions.	✓	✓	✓
Date	Standard of care may vary across time.	✓	✓	✓
<i>Patient characteristics</i>				
Distribution of TEMs	Differences in the distribution of TEMs impacts method choice. PAIC can only adjust for differences if there is sufficient overlap in distribution.	✓	✓	✓
Distribution of PVs	PAIC can only adjust for differences in distribution of PV if there is sufficient overlap in distribution.			✓
<i>Treatment characteristics of common comparators</i>				
Dosage	Common comparators should be administered at the same dosage unless dose-response curve flattens after certain dose.	✓	✓	
Route of administration	Common comparators should be administered in similar manner if route of administration impacts efficacy.	✓	✓	
Duration	Common comparators should be delivered over similar length of time or have similar discontinuation rules.	✓	✓	
<i>Outcome characteristics</i>				
Criteria for event	Similar criteria should be used to define an event.	✓	✓	✓
Assessor	Investigator-assessed outcomes may be more prone to bias than blinded independent committee.	✓	✓	✓

Criteria	Rationale	Relevant for...		
		NMA	Anchored PAIC	Unanchored PAIC
Start and end point of measurement	Time-to-event endpoints should be measured from similar starting point (e.g., randomization) and have similar censoring rules.	✓	✓	✓
Frequency of measurement	Differences in the frequency of assessment of progression outcomes between trials will lead to time-assessment bias [5].			✓

Abbreviations: AAP, abiraterone acetate and prednisone; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PAIC, population-adjusted comparison; PHA, proportional hazards assumption PV, prognostic variable; RCT, randomized controlled trial; RTE, relative treatment effect; TEM, treatment effect modifier

1.2.1. Study characteristics

There are several aspects to a study's characteristics that may introduce bias in an indirect treatment comparison (ITC). For example, within study-bias related to a study's conduct such as blinding and concealment of randomization directly impacts the observed outcomes, and this bias will manifest itself to the ITC. Randomization only holds within a subgroup if the study stratified patients by the subgroup during randomization; if the PVs between treatment arms are imbalanced within a subgroup of interest, then this negates the benefit of conducting anchored ITCs. In addition, the geography of a study may impact a study's external validity since quality and standard of care may vary across regions. Furthermore, differences in follow-up duration and data maturity may introduce bias when the relative effects for a particular outcome are expected to vary over time. Finally (but not exclusively), treatment crossover will bias outcomes experienced after crossover such as death.

All four included studies were phase 3 RCTs (Table S3). PROfound was an open-label trial, while all others were double-blinded studies. In all studies, the concealment of randomization was considered to be adequate. *BRCA* mutation status was recorded in all trials, yet MAGNITUDE was the only trial to stratify by *BRCA* mutation status. All studies were conducted on a global scale. The maximum duration of most included studies was shorter than MAGNITUDE (i.e., 66 months). The maximum duration ranged from 47 months (TALAPRO-2) to 66 months (MAGNITUDE). In terms of data maturity, the final results for overall survival (OS) were available for all trials except TALAPRO-2.

Among these noted differences, there was one key issue that challenged the validity of any ITC: the measurement and stratification of *BRCA* mutation status during randomization. Since the *BRCA*-positive subgroup was included within the target patient population, ITCs within this subgroup should be prioritized. However, only MAGNITUDE stratified by *BRCA* mutation status when randomizing patients. Thus, randomization was broken in any comparator trial that reported outcomes in the *BRCA*-positive subgroup, biasing any anchored ITC which relies on PVs being balanced across arms within trials.

Table S3: Study characteristics of MAGNITUDE and other PARPi RCTs (PROpel, PROfound, TALAPRO-2)

	MAGNITUDE	PROpel	PROfound	TALAPRO-2
Study design	RCT	RCT	RCT	RCT
Trial phase	Phase 3	Phase 3	Phase 3	Phase 3
Blinding	Double	Double	Open label	Double
Concealment of randomization	Adequate	Adequate	Adequate	Adequate
Recorded patients' BRCA mutation status	Yes	Yes	Yes	Yes
Stratified by BRCA mutation status during randomization	Yes	No	No	No
Number of patients	<u>Cohort 1: HRR+ (BRCA+)</u> Niraparib + AAP: 212 (113) Placebo + AAP: 211 (112)	<u>All comer (BRCA+)</u> Olaparib + AAP: 399 (47) Placebo + AAP: 397 (38)	<u>Cohort A: BRCA+/ATM+ (BRCA+)</u> Olaparib: 162 (102) Enzalutamide or AAP: 83 (58) <u>Cohort B (other HRR mutations)</u> Olaparib: 94 Enzalutamide or AAP: 48	<u>Cohort 1: All comer (BRCA+)</u> Talazoparib + E: 402 (27) Placebo + E: 403 (32) <u>Cohort 2: HRR+ (BRCA+)</u> Talazoparib + E: 200 (71) Placebo + E: 199 (84)
Location	Global	Global	Global	Global
Maximum duration (months)	66	48	48	47
Follow-up durations and maturity of data				
Median of survival follow-up (months)	<u>Cohort 1: HRR+</u> IA1: 18.6 IA2: 26.8 Final: 37.3 <u>Cohort 1: BRCA+</u> IA1: 16.7 IA2: 24.8 Final: 35.9	<u>Among censored: All comer</u> IA1: 22.2 (O+AAP), 21.8 (AAP) IA2: 30.0 (O+AAP), 29.4 (AAP) Final: 36.6 (O + AAP), 36.5 (AAP)	<u>Among censored:</u> <u>Cohort A: BRCA+/ATM+</u> IA1: 12.6 (O), 13.2 (E or AAP) Final: 21.9 (O), 21.0 (E or AAP) <u>Cohort B: other HRR mutations</u> IA1: NR Final: 18.7 (O), 18.3 (E or AAP)	NR [for rPFS follow-up: <u>Cohort 1: All comer</u> IA1: 24.9 (T + E), 24.6 (E) <u>Cohort 2: HRR+</u> IA1: 17.5 (T + E), 16.8 (E)]
% of deaths required for planned final analysis	<u>Cohort 1: HRR+ (not planned for BRCA+)</u> IA1: 114/246, 46.3% IA2: 179/246, 72.8% Final: 240/246, 97.6%	<u>All comer</u> NR; final analysis planned to take place 48 months after first person randomized	<u>Cohort A: BRCA+/ATM+</u> IA1: 93/147, 63.3% Final: 148/147, 100.7%	<u>Cohort 1: All comer</u> IA1: 252/438, 57.5%
Median survival (months)	<u>Cohort 1: HRR+</u> IA1: NE (N + AAP), NE (AAP) IA2: 29.3 (N + AAP), 32.2 (AAP)	<u>All comer</u> IA1: NE (O + AAP), NE (AAP) IA2: NE (O + AAP), NE (AAP) Final: 42.1 (O + AAP), 34.7 (AAP)	<u>Cohort A: BRCA+/ATM+</u> IA1: 18.5 (O), 15.1 (E or AAP) Final: 19.1 (O), 14.7 (E or AAP) <u>Cohort B: other HRR mutations</u>	<u>Cohort 1: All comer</u> IA1: 36.4 (T + E), NE (E) <u>Cohort 2: HRR+</u> IA1: NE (T + E), 33.7 (E)

	Final: 30.4 (N + AAP), 31.0 (AAP) <u>Cohort 1: BRCA+</u> IA1: NE (N + AAP), NE (AAP) IA2: 29.3 (N + AAP), 28.6 (AAP) Final: 30.4 (N + AAP), 28.6 (AAP)		IA1: 14.2 (O), 11.5 (E or AAP) Final: 14.1 (O), 11.5 (E or AAP)	
Treatment cross-over				
Cross-over criteria	Not permitted	Not permitted	Permitted (to intervention arm)	Not permitted

Abbreviations: AAP, abiraterone acetate plus prednisone; E, enzalutamide; HRR, homologous recombination repair; IA, interim analysis; N/A, not applicable; NE, not estimable; NR, not reported; O, olaparib; RCT, randomized controlled trial; rPFS, radiographic progression-free survival; T, talazoparib

1.2.2. Population

The appropriateness and validity of an ITC method depends on whether there are differences in the distribution of treatment effect modifiers (TEM) across trials, as well as prognostic variables (PV) in the case of unanchored comparisons. When there are differences, population-adjusted indirect comparison methods such as the matching-adjusted indirect comparison (MAIC) may be used to adjust for these differences, provided there is enough overlap between MAGNITUDE and the populations of the comparator trials. Differences between trial populations arise from differences in trial eligibility criteria, and the distribution of TEMs and PVs may be inspected through comparison of baseline characteristics.

In preparation for the ITC feasibility assessment, a list of TEMs and PVs was developed based on published prognostic models and statistical analyses of MAGNITUDE data. This list is not exhaustive and needs to be formally validated.

A prognostic model for predicting OS in patients with 1L mCRPC was utilized by the United States Food and Drug Administration (FDA) in an Oncologic Drugs Advisory Committee Meeting for olaparib plus abiraterone acetate with prednisone (AAP); the model identified albumin, alkaline phosphatase (ALP), disease site, Eastern Cooperative Oncology Group (ECOG) performance status (PS), hemoglobin, lactate dehydrogenase (LDH), opioid use, and prostate-specific antigen (PSA) as PVs [6, 7].

Multivariate analyses from MAGNITUDE explored the influence of PVs [8]. Baseline PSA value ($p=0.002$), LDH ($p=0.023$), ALP ($p=0.041$), and the presence of visceral disease ($p=0.003$) were significant PVs for radiographic progression-free survival (rPFS) by blinded independent central review (BICR) [8]. Baseline PSA value ($p=0.029$), LDH ($p<0.001$), ALP ($p=0.005$), age ($p=0.002$), ECOG PS ($p=0.033$), the number of bone lesions at baseline ($p=0.002$), and the presence of visceral disease ($p=0.016$) were statistically significant PVs for OS [8].

Subgroup analyses within MAGNITUDE suggested that BRCA mutation status, presence of visceral metastases, and baseline PSA were potential TEMs. Additionally, line of therapy, prior treatment, ECOG PS, Gleason score, and baseline pain were identified as potential TEMs.

A summary of these TEMs and PVs is presented in Table S4.

Table S4: Potential treatment effect modifiers and prognostic variables reported in at least one comparator trial

Treatment effect modifiers	Prognostic variables
• BRCA1 mutation status • BRCA2 mutation status • ECOG PS • Gleason score • Line of therapy • Pain • Presence of visceral metastases • Prior treatment • Prostate-specific antigen	• Age • Albumin • Alkaline phosphatase • Disease site • ECOG PS • Hemoglobin • Lactate dehydrogenase • Number of bone lesions • Opioid use

Treatment effect modifiers	Prognostic variables
	• Presence of visceral metastases • Prostate-specific antigen

Abbreviations: ARSi, androgen-receptor signaling inhibitors; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; PS, performance status; PSA, prostate-specific antigen

An overview of each trial's eligibility criteria is presented in Table S5. All trials recruited patients at least 18 years of age. Studies either included patients with an ECOG PS of 0-1 or 0-2. Cohort 1 of MAGNITUDE, PROfound, and Cohort 2 of TALAPRO-2 recruited patients with HRR mutations. Symptomatic status (asymptomatic or mildly symptomatic mCRPC) was an inclusion criterion for MAGNITUDE and TALAPRO-2. No other trials specified eligibility criteria for symptomatic status. All trials required detection of metastatic lesion either on bone scan or CT or MRI.

Further details on prior and concomitant treatment restrictions are available in Table S6. MAGNITUDE recruited 1L mCRPC patients but allowed them to receive AAP in the mCRPC setting within four months of randomization to allow for genetic testing – these patients must have no evidence of PSA progression during the screening period. Nevertheless, apart from PROfound, no other trials permitted AAP as mCRPC therapy prior to randomization, and these differences must be considered in any unanchored population-adjusted ITCs, since prior AAP is a PV. While PROfound recruited 1L+ mCRPC patients, >96% of the included patients were randomized to 2L or later therapy. Since line of therapy is a TEM, differences in line of therapy need to be adjusted for in a population-adjusted ITC to avoid bias. All other trials recruited 1L mCRPC patients.

In this ITC feasibility assessment, standardized mean differences (SMD) in baseline characteristics of comparator studies vs. MAGNITUDE were compared, where an absolute SMD > 0.2 was considered as notable differences (Table S7). Among *BRCA*-positive patients receiving olaparib monotherapy in PROfound, there were more Asian patients, fewer patients with an ECOG PS score of 0, more patients with an ECOG PS of 2, fewer patients with Gleason score ≥ 8 , and more patients with a Brief Pain Inventory-Short form item #3 (BPI-SF3) score ≥ 4 compared with *BRCA*-positive patients receiving niraparib plus AAP in MAGNITUDE. Among the *BRCA*-positive patients receiving olaparib plus AAP in PROpel, there were more patients with an ECOG PS of 0, fewer patients with an ECOG PS of 1, more patients with bone only metastases, and more patients with a BPI-SF3 score ≥ 4 compared with the *BRCA*-positive patients receiving niraparib plus AAP in MAGNITUDE. There were no notable differences in the reported baseline characteristics of HRR-positive patients receiving talazoparib plus enzalutamide in TALAPRO-2 and *BRCA*-positive patients receiving niraparib plus AAP in MAGNITUDE.

While there are some differences in the measured covariates noted above, these may be adjusted for in a population-adjusted ITC. There are, however, unreported PVs such as baseline ALP, LDH, and number of bone lesions in PROpel, PROfound, and TALAPRO-2; any imbalances between MAGNITUDE and comparator trials in these unreported PVs cannot be assessed or adjust for, leading to uncertainty in the robustness of any potential unanchored ITCs.

Table S5: Overview of inclusion/exclusion criteria

Study	Interventions	Age (years)	ECOG PS	Line of therapy	Gene alterations	Prostate cancer status at study entry	Prostate cancer progression criteria	Pain	PSA value	Type of metastases
MAGNITUDE (NCT03748641)	Niraparib + AAP AAP	≥ 18	0 – 1	1L	Positive for HRR gene alteration (Cohort 1 & 3). (BRCA+ subgroup available)	Histologically confirmed prostate cancer with documented metastases and testosterone levels ≤50 ng/dL	RECIST 1.1 (soft tissue lesions) PCWG3 (bone lesions)	BPI-SF Q3 score ≤3.	NR	Metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI.
PROfound (NCT02987543)	Olaparib AAP or Enzalutamide	≥ 18	0 – 2	1L+	Qualifying HRR mutation in tumor tissue by the Lynparza HRR Assay. (BRCA+ subgroup available)	Histologically confirmed prostate cancer with documented metastases, progressive disease, and testosterone levels ≤50 ng/dL	RECIST 1.1 (soft tissue; lymph nodes) NR (radiographic)	NR	NR	Documented metastatic lesion on either bone scan or CT/MRI scan.
PROpel (NCT03732820)	Olaparib + AAP AAP + Placebo	≥ 18	0 – 1	1L	NR (BRCA+ subgroup available)	Histologically or cytologically confirmed prostate cancer with metastatic, progressive disease, and testosterone levels ≤50 ng/dL	RECIST 1.1 (soft-tissue disease) PCWG3 (bone or PSA)	NR	NR	Documented metastatic lesion on either a bone scan or a CT/MRI scan.
TALAPRO-2 (NCT03395197)	Talazoparib + Enzalutamide Enzalutamide	≥ 18	0 – 1	1L	Patients harboring HRR alterations (Cohort 2)	Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features, with metastases, progressive disease, and testosterone levels ≤50 ng/dL	RECIST 1.1 (soft tissue) PCWG3 (bone) PSAWGb (PSA)	Asymptomatic or mildly symptomatic mCRPC.	NR	Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan.

^a ECOG 0-2 assumed as Karnofsky performance status scores were ≥60%.

^b Assumed, as criteria was in line with PSAWG.

Abbreviations: 1L, first line; AAP, abiraterone acetate plus prednisone; BPI-SF Q3: Brief Pain Inventory–Short Form Question 3; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; NR, not reported; PCWG(2/3), Prostate Cancer Working Group criteria (version 2/3); PS, performance status; PSA, prostate-specific antigen; PSAWG, Prostate Specific Antigen Working Group criteria; RECIST, Response Evaluation Criteria in Solid Tumours

Table S6: Overview of restrictions on prior and concomitant treatment

Study	Permitted prior or concomitant treatment	Prohibited prior or concomitant treatment	Line of mCRPC therapy
MAGNITUDE (NCT03748641)	- GnRHa or bilateral orchiectomy - AAP in the mCRPC setting up to four months prior to randomization to allow for genetic testing; these patients must not have evidence of PSA progression (by PCWG3) at screening. - Prior taxane based chemotherapy for mHSPC and prior ARSi for nmCRPC or mHSPC (no abiraterone) was allowed.	- No prior treatment with a PARP inhibitor - No prior systemic therapy (i.e., novel second-generation AR targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy, or more than 4 months of AAP prior to randomization) in the mCRPC setting; or AAP outside of the mCRPC setting	1L
PROfound (NCT02987543)	- Progressed during treatment with enzalutamide or abiraterone, administered for (m)CRPC or mHSPC - Previous taxane chemotherapy was allowed - Men without previous surgical castration were required to continue luteinizing-hormone-releasing hormone analogue therapy	N/A	1L+
PROpel (NCT03732820)	- ADT and first-generation antiandrogen agents permitted in mCRPC first-line setting with a 4-week washout period - Docetaxel during neoadjuvant/adjuvant treatment for localized prostate cancer and mHSPC was permitted	No prior systemic treatment in the mCRPC first-line setting	1L
TALAPRO-2 (NCT03395197)	- The following agents are NOT exclusionary if received for CSPC: docetaxel, biologic therapy (e.g., sipuleucel-T), or radionuclide therapy, if discontinued 28 days prior to day 1 (part 1) or randomization (part 2); hormonal therapy (e.g., bicalutamide, nilutamide, flutamide, estrogens) or abiraterone, if discontinued prior to randomization - The following agents are NOT exclusionary if received for CRPC: ADT and first-generation anti-androgens	- No prior systemic cancer treatment initiated in the non-metastatic CRPC or mCRPC disease state - No prior treatment with second-generation AR inhibitors (enzalutamide, apalutamide and darolutamide), a PARP inhibitor, cyclophosphamide or mitoxantrone for prostate cancer - No prior treatment with platinum-based therapy ≤ 6 months (from the last dose) or any history of disease progression on platinum-based therapy ≤ 6 months (from the last dose) - Prednisone > 10 mg/day (or equivalents) is exclusionary	1L

Abbreviations: 1L, first line; AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; AIPC, androgen-independent prostate cancer; AR, androgen receptor; CSPC, castration-sensitive prostate cancer; GnRHa, gonadotropin-releasing hormone agonist; LHRH, luteinizing hormone-releasing hormone; (m)CRPC, (metastatic) castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; N/A, not applicable, NR, not reported; PARP, poly-ADP ribose polymerase; PCWG(3), Prostate Cancer Working Group criteria (version 3); PSA, prostate-specific antigen

Table S7: Baseline characteristics of MAGNITUDE and other PARPi RCTs (PROpel, PROfound, TALAPRO-2)

[illegible]

M1 disease at diagnosis (%)														
Yes	61.9	44.6									48	-0.28	48	-0.28
Gleason score at diagnosis (%)														
≥ 8	74.1	64.3	72.4	-0.04	65.8	-0.18	65	-0.20	64	-0.22	76.0	0.04	71.9	-0.05
BPI-SF #3 score at baseline (%)														
0	50.0	50.9												
1 – 3	45.5	35.7												
≥ 4	4.5	13.4	31.9	0.76	26.3	0.63	34.3	0.81	44.8	1.06				

Notes: SMDs calculated between comparator and niraparib plus AAP; absolute SMDs >0.2 are **bolded**. Blank cells indicate covariate not reported.

Abbreviations: AAP, abiraterone acetate plus prednisone; BPI-SF, Brief Pain Inventory-Short Form; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; PARPi, poly-ADP ribose polymerase inhibitor; RCT, randomized controlled trial; SMD, standardized mean difference; ULN, upper limit of normal

1.2.3. Interventions and comparators

Anchored ITCs via a common comparator are preferred over unanchored ITCs. Nevertheless, their validity depends on the similarity of a common comparator between trials. Any factors that could impact its effect (e.g., dosage, route of administration), and in turn the relative effects inputted into an ITC, need to be considered. Duration of treatment also needs to be considered if the relative effects (in the case of anchored comparisons) or absolute effects (in the case of unanchored comparisons) are expected to vary over time.

In total, 7 unique therapies were compared in the included studies (Table S8). AAP was the only common comparator, and there were no concerning differences in the treatment characteristics between MAGNITUDE and PROpel.

Table S8: Treatment characteristics of all included studies

Intervention	Study	Dosage	Route of administration	Median treatment exposure	Treatment duration
Niraparib + AAP	MAGNITUDE	Niraparib + AA: 200 mg/500 mg, once daily P: 5 mg, twice daily	oral	IA1: 13.8 months (HRR+) IA2: 17.9 months (HRR+) Final: 20.2 months (HRR+), 20.5 months (BRCA+)	Until study drug-related toxicity or radiographic progression & alternate treatment initiation.
AAP	MAGNITUDE	AA: 1000 mg, once daily P: 5 mg, twice daily	AA: oral P: oral	IA1: 12.1 months (HRR+) IA2: 15.2 months (HRR+) Final: 15.2 months (HRR+), 14.4 months (BRCA+)	Until study drug-related toxicity or radiographic progression & alternate treatment initiation.
	PROpel	AA: 1000mg, once daily P: 5mg, twice daily	AA: oral P: oral	Final: 15.7 months	Until unequivocal radiographic progressive disease is assessed by investigator (using [RECIST 1.1] for soft tissue lesions and [PCWG 3] criteria for bone lesions), unacceptable toxicity occurs, or the patient withdraws consent.
Enzalutamide	TALAPRO-2	160 mg, once daily	oral	Cohort 1, IA1: 16.6 months Cohort 2, IA1: 12.1 months	Until radiographic progression is determined (by BICR) unless in the opinion of the investigator the patient is still deriving benefit at this time, or following radiographic progression the patient is no longer clinically benefitting in the opinion of the investigator, or an adverse event leading to permanent discontinuation, or patient decision to discontinue study treatment, or death.
Investigator's choice of AAP or enzalutamide	PROfound	AA: 1000 mg, once daily P: 5 mg, twice daily E: 160 mg, once daily	AA: oral P: oral	3.9 months	Until objective radiographic progression (BICR), unable to tolerate, alternative anticancer therapy due to unequivocal clinical progression.
Olaparib	PROfound	300 mg, twice daily	oral	7.4 months	Until objective radiographic progression (BICR), unable to tolerate, alternative anticancer therapy due to unequivocal clinical progression
Olaparib + AAP	PROpel	Olaparib: 300mg, twice daily AA: 1000mg, once daily P: 5mg, twice daily	oral	Final O: 18.5 months AAP: 20.1 months	Until unequivocal radiographic progressive disease is assessed by investigator (using [RECIST 1.1] for soft tissue lesions and [PCWG 3] criteria for bone lesions), unacceptable toxicity occurs, or the patient withdraws consent.

Intervention	Study	Dosage	Route of administration	Median treatment exposure	Treatment duration
Talazoparib + enzalutamide	TALAPRO-2	Talazoparib: 0.5mg, once daily Enzalutamide: 160mg, once daily	T: oral E: oral	Cohort 1, IA1: T: 19.8 months E: 22.2 months Cohort 2, IA1: T: 14.6 months E: 14.7 months	Until radiographic progression is determined (by BICR) unless in the opinion of the investigator the patient is still deriving benefit at this time, or following radiographic progression the patient is no longer clinically benefitting in the opinion of the investigator, or an adverse event leading to permanent discontinuation, or patient decision to discontinue study treatment, or death.

Abbreviations: AA, abiraterone acetate; AAP, abiraterone acetate plus prednisone; BICR, blinded, independent central review; C, cabazitaxel; D, docetaxel; E, enzalutamide; HRR, homologous recombination repair; IA, interim analysis; O, olaparib; P, prednisone; PCWG, Prostate Cancer Working Group; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; T, talazoparib

1.2.4. Outcomes

The availability of outcomes and statistics reported by each trial influence whether an ITC is possible, while the comparability of outcome measurements influences the validity of ITCs. Within RCTs, interventions are compared using the exact same criteria for each outcome of interest. However, these criteria may vary between trials, potentially leading to bias in ITCs. The criteria used to define an event, the person(s) who assessed the criteria for an event, and observation period may influence the observed effects. In addition, for unanchored ITCs, differences in the frequency of event assessments may bias time-to-event outcomes.

A summary of the criteria used to evaluate the outcomes of interest in each trial are provided in Table S9. All trials used PCWG3 criteria to assess radiographic and PSA progression.

The availability of outcomes of interest is summarized in Table S10. All trials reported rPFS and OS in the *BRCA+* subgroup; however, TALAPRO-2 has only reported hazard ratios.

Table S9: Summary of outcome measurements in MAGNITUDE and other PARPi RCTs (PROpel, PROfound, TALAPRO-2)

	MAGNITUDE	PROpel	PROfound	TALAPRO-2
rPFS				
Soft tissue lesion criteria	RECIST 1.1	RECIST 1.1	RECIST 1.1	RECIST 1.1
Bone lesion criteria	PCWG3	PCWG3	PCWG3	PCWG3
Assessor	BICR Investigator	BICR Investigator	BICR Investigator	BICR
Outcome definition	Time from randomization date to date of radiographic progression or death, whichever occurs first.	Time from randomization to radiological progression, or death from any cause, whichever occurs first.	Time from randomization until the date of objective radiological disease progression regardless of whether the patient withdrew from randomized therapy or received another anti-cancer therapy prior to progression.	Time from the date of randomization to first objective evidence of radiographic progression, or death due to any cause, whichever occurs first.
Frequency of assessment	Baseline, weeks 9, 17, 25, and every 12 weeks thereafter.	Baseline, weeks 8, 16, 24, and every 12 weeks thereafter.	Baseline and every 8 weeks thereafter.	Every 8 weeks up to week 25, and every 12 weeks thereafter.
Overall survival				
Outcome definition	Time from date of randomization to date of death from any cause.	Time from randomization to death from any cause.	Time from randomization to death from any cause.	Time from randomization to death from any cause.
Time to PSA progression				
Outcome definition	Time from date of randomization to the first date of documented PSA progression based on PCWG3 criteria.	Time from randomization to PSA progression per PCWG3 criteria.	NR	Time from baseline to PSA progression per PCWG3 criteria.
Frequency of assessment	Baseline, every 4 weeks in first year, every 8 weeks in second year, every 12 weeks beyond until treatment discontinuation.	Baseline, every 4 weeks.	NR	Baseline, every 8 weeks.
Time to second progression (PFS2) on next line				
Outcome definition	Time from randomization to the date of first progression on the	Time from randomization to second progression by	Time from randomization to second progression by	Time from randomization to the date of documented progression

	first subsequent therapy, or death from any cause, whichever occurred first.	investigator assessment of radiographic or clinical progression, or death.	investigator assessment of radiological or clinical progression or death.	based on investigator assessment on the first subsequent antineoplastic therapy, or death from any cause, whichever occurs first.
Frequency of assessment	Every month until cycle 3 then every 3 months.	Every 12 weeks following first progression event.	Every 12 weeks following first progression event.	Every 8 weeks up to week 25 after randomization, and every 12 weeks thereafter; if this is not possible, as per local standard of care.
Time to subsequent therapy				
Outcome definition	Time from the date of randomization to the date of subsequent anti-cancer therapy for prostate cancer.	Time from randomization to first subsequent anticancer therapy after discontinuation of randomized treatment or death from any cause (whichever was earlier).	NR	Time from randomization to the first use of antineoplastic therapy. Such therapies include cytotoxic chemotherapy, hormonal chemotherapy, and investigational agents for prostate cancer.
Time to treatment discontinuation				
Outcome definition	Time from treatment commencement to the date of treatment discontinuation due to any cause including death	NR	NR	NR

Abbreviations: AQA, Analgesic Quantification Algorithm; BICR, blinded, independent central review; BPI-SF, Brief Pain Inventory– Short Form; NR, not reported; PCWG3, Prostate Cancer Working Group criteria (version 3); PSA, prostate-specific antigen; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival

Table S10: Data availability for efficacy outcomes of interest

	MAGNITUDE BRCA+ only	PROpel BRCA+ only	All-comer	PROfound BRCA+ only	Cohort A (BRCA+/ ATM+)	Cohort B (other HRR+)	Cohort A + B (HRR+)	TALAPRO2 BRCA+ only	Cohort 1 (All comer)	Cohort 2 (HRR+)
rPFS – BICR	✓	✓	✓	✓	✓	✓	✓	HR only	✓	✓
rPFS – Investigator	✓	✓	✓		HR only	HR only	HR only		✓	✓
Overall survival	✓	✓	✓	✓	✓	✓	✓	HR only	✓	✓
Time to PSA progression	✓	✓	HR only						✓	✓
Time to second progression (PFS2) on next line	✓	✓	✓		✓	✓	✓		✓	✓
Time to subsequent therapy	✓	✓	✓						HR only	
Time to treatment discontinuation	✓									

Note: A checkmark (✓) indicates a Kaplan-Meier curve is available for the time-to-event outcome. If only a HR is available, this is noted.

Abbreviations: 2L, second line; BICR, blinded, independent central review; BPI-SF, Body pain index– short form; HR, hazard ratio; rPFS, radiographic progression-free survival

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