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REVIEW

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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ABSTRACT

Introduction: Poly(ADP-ribose) polymerase inhibitors (PARPi) are a novel option to treat patients with metastatic castration-resistant prostate cancer (mCRPC). Niraparib plus abiraterone acetate and prednisone (AAP) is indicated for *BRCA1/2* mutation-positive mCRPC. Niraparib plus AAP demonstrated safety and efficacy in the phase 3 MAGNITUDE trial (NCT03748641). In the absence of head-to-head studies comparing PARPi regimens, the feasibility of conducting indirect treatment comparisons (ITC) to inform decisions for patients with first-line *BRCA1/2* mutation-positive mCRPC has been explored.

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Methods: A systematic literature review was conducted to identify evidence from randomized controlled trials on relevant comparators to inform the feasibility of conducting ITCs via network meta-analysis (NMA) or population-adjusted indirect comparisons (PAIC). Feasibility was assessed based on network connectivity, data availability in the *BRCA1/2* mutation-positive population, and degree of within- and between-study heterogeneity or bias.

Results: NMAs between niraparib plus AAP and other PARPi regimens (olaparib monotherapy, olaparib plus AAP, and talazoparib plus enzalutamide) were inappropriate due to the disconnected network, differences in trial populations related to effect modifiers, or imbalances within *BRCA1/2* mutation-positive subgroups. The latter issue, coupled with the lack of a common comparator (except for olaparib plus AAP), also rendered anchored PAICs infeasible. Unanchored PAICs were either inappropriate due to lack of population overlap (vs. olaparib monotherapy) or were restricted by unmeasured confounders and small sample size (vs. olaparib plus AAP). PAIC versus talazoparib plus enzalutamide was not possible due to lack of published arm-level baseline characteristics and sufficient efficacy outcome data in the relevant population.

Conclusion: The current randomized controlled trial evidence network does not permit robust comparisons between niraparib plus AAP and other PARPi regimens for patients with 1L *BRCA*-positive mCRPC. Decision-makers should scrutinize any ITC results in light of their limitations. Real-world evidence combined with clinical experience should inform treatment recommendations in this indication.

Keywords: *BRCA*; Indirect treatment comparisons; Metastatic castration-resistant prostate cancer; Network meta-analysis; Niraparib plus abiraterone acetate dual-action tablet; PARPi; Population-adjusted indirect comparisons

Key Summary Points

Why carry out this study?

Head-to-head studies between niraparib plus abiraterone acetate and prednisone (AAP) and other poly(ADP-ribose) polymerase inhibitor (PARPi) combinations or monotherapy approved for the treatment of patients with *BRCA1/2* mutation-positive metastatic castration-resistant prostate cancer (mCRPC) are not available.

To inform clinical and reimbursement decisions for patients with *BRCA1/2* mutation-positive mCRPC, indirect treatment comparisons (ITC) using evidence from PARPi randomized controlled trials may fill this evidence gap; however, the study designs and populations of PARPi randomized controlled trials (RCT) are heterogeneous, particularly in terms of the testing and stratification of *BRCA1/2* mutations; therefore, the feasibility of conducting robust ITCs is warranted.

The study aimed to determine if results from available and/or published trials were sufficient to construct an evidence network to allow for robust ITCs between first-line PARPi regimens among patients with *BRCA1/2* mutation-positive mCRPC.

What was learned from the study?

The available evidence was insufficient to allow for ITCs between niraparib plus AAP and two PARPi regimens (olaparib monotherapy, and talazoparib plus enzalutamide), and unanchored population-adjusted indirect comparison (PAIC) was only considerable between niraparib plus AAP and olaparib plus AAP; however, the limitations of this analysis imply that its robustness was unclear.

The robustness of any existing or future ITC of PARPis for treating patients with *BRCA1/2* mutation-positive mCRPC should be rigorously assessed and any limitations should be acknowledged.

To determine the best therapeutic option for patients with *BRCA1/2* mutation-positive mCRPC, RCTs should be explicitly designed to evaluate the comparative efficacy and safety of treatments in this population.

INTRODUCTION

Prostate cancer (PC) is the second-most common cancer among men worldwide, accounting for approximately 375,304 deaths in 2020 [1]. This clinically heterogeneous disease exhibits distinct genetic, molecular, and clinical characteristics wherein excessive and aberrant prostate growth leads to the metastatic tumor formation [2]. Trans women and non-binary people born male can also develop PC. Up to one-half of patients with PC will progress to metastatic castration-resistant PC (mCRPC), an aggressive, incurable form of the disease [3]. Despite recent improvements in available therapies, mCRPC is associated with a high mortality rate [4–7].

Up to 30% of patients with mCRPC harbor alterations in genes associated with DNA damage repair including homologous recombination repair (HRR) genes such as *BRCA1* and *BRCA2*, which are associated with poor clinical outcomes and resistance to commonly used therapies [8–11]. The primary treatment goal in the first-line (1L) setting for the *BRCA1/2* mutation-positive (hereafter, "*BRCA*-positive") mCRPC population is to maintain quality of life by prolonging time until disease progression. However, the best therapeutic option to achieve this is unclear, and there remains a high unmet need for novel therapies.

Increasing evidence suggests that patients with mCRPC harboring *BRCA1/2* alterations represent a distinct molecular subtype of mCRPC with a more aggressive, faster disease progression, and premature death [8–10, 12]. In three ongoing randomized controlled trials (RCTs), median time to radiographic progression ranged from 8.4 to 11.0 months among patients who are *BRCA*-positive receiving abiraterone acetate or enzalutamide alone, respectively [4, 13, 14]. A recent observational study compared patients who are *BRCA*-positive and *BRCA*-negative receiving current androgen-receptor signaling inhibitors (ARSi; i.e., abiraterone, enzalutamide) or taxane therapies (i.e., cabazitaxel or docetaxel),and patients who were *BRCA*-positive had shorter median time to radiographic progression (7.1 months vs. 10.3 months) and death (19.4 months vs. 27.9 months) than patients who were *BRCA*-negative [12].

Current guidelines recommend various treatments for the mCRPC population [15–18], but more recently have incorporated specific recommendations for the *BRCA*-positive subpopulation, in large part due to the advent of poly(ADP-ribose) polymerase inhibitors (PARPi) (e.g., olaparib, niraparib, talazoparib) that target underlying mutations in the HRR pathway (specifically *BRCA1/2)* [19]. Although ARSis and taxanes are considered the standard 1L treatment for newly diagnosed mCRPC [15–17, 20], a clear benefit was demonstrated for treatment with PARPis as monotherapy (after chemotherapy or ARSi) or combined with ARSis over docetaxel or ARSis alone in patients with *BRCA*-positive mCRPC, making a strong case for PARPis to be considered the first treatment choice in this population [4, 5, 8, 21, 22].

Niraparib is an orally administered, highly selective PARPi, leading to cell death through synthetic lethality [23, 24]. Abiraterone acetate, a pro-drug of abiraterone which is an oral, androgen biosynthesis (CYP17) inhibitor, blocks testosterone creation in the testes, adrenal gland, and tumor cells [25]. Based on results from the MAGNITUDE trial (NCT03748641) [4, 23], niraparib plus abiraterone acetate dual-action tablet (DAT) in combination with prednisone received market authorization in 2023 in the United States (US) for adults with mCRPC harboring *BRCA1/2* mutations [26], and in Europe and Canada for adults with mCRPC harboring *BRCA1/2* mutations for whom chemotherapy is not indicated [27, 28]; in Canada, the label stipulates the intended population as asymptomatic/mildly symptomatic [28]. MAGNITUDE, a phase 3 randomized, double-blind, placebo-controlled, multicenter study, evaluated the efficacy and safety of niraparib and abiraterone acetate in combination with prednisone (AAP) as 1L treatment for patients with mCRPC with or without HRR mutations; the greatest benefit was observed in the *BRCA*-positive subgroup [4, 23].

Several other PARPi monotherapy (i.e., olaparib [5], rucaparib [22]) and combination

therapies (i.e., olaparib plus AAP [8], talazoparib plus enzalutamide [21]) are promising targeted treatment options for patients with *BRCA*-positive mCRPC. However, head-to-head comparisons from RCTs are lacking for niraparib plus AAP versus other PARPi monotherapy and combination therapies. Indirect treatment comparisons (ITC) are thus necessary to provide comparative efficacy evidence to support treatment and reimbursement decision-making.

This study assessed the feasibility of conducting ITCs of niraparib plus AAP versus other PARPi therapies as 1L treatment for patients with *BRCA*-positive mCRPC based on individual patient data (IPD) in MAGNITUDE and published aggregate data in comparator studies identified via a systematic literature review (SLR).

METHODS

SLR

An SLR was conducted on 14 March 2023 to identify RCTs of niraparib plus AAP and relevant comparators used as 1L treatment of adults with *BRCA*-positive mCRPC. The SLR followed the methodological guidance from the National Institute for Health and Care Excellence (NICE), the Cochrane Collaboration, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [29–31]. Electronic literature databases and relevant conference proceedings were searched for studies based on pre-specified eligibility criteria (Table S1). Title/abstract and full-text screening were performed by two independent reviewers. Data from included articles were extracted by one reviewer and validated by a second, senior reviewer. Across all levels, discrepancies were resolved by a third reviewer. Additional details on the SLR methodology are provided in the electronic supplementary material (Tables S1–S10).

Selection of ITC Methods

Several methods (which each require a different set of assumptions) can be used to conduct an ITC when IPD are obtainable for all or some of the studies (Fig. 1). In this study, IPD from MAGNITUDE and aggregate-level data from RCTs identified in the SLR were available to inform the ITCs. The ITC methods were prioritized based on NICE guidance, which states a preference for methods that limit assumptions and ease interpretability for decision-making: (1) network meta-analysis (NMA), (2) anchored population-adjusted indirect comparison (PAIC), and (3) unanchored PAIC [32]. An overview of these methods is presented in Fig. 2.

Identification of Treatment-Effect Modifiers and Prognostic Variables

The feasibility assessment required investigation of the presence and distribution of treatment–effect modifiers (TEM) and prognostic variables (PV) across RCTs (Fig. 1); therefore, potential TEMs and PVs were identified a priori [33]. The list used in this study was based on a published prognostic model used by the US Food and Drug Administration [34, 35] and statistical analyses of MAGNITUDE data.

Assessing Feasibility of an NMA

Four key criteria had to be met to assess the appropriateness of using NMA to facilitate the ITCs: (1) a connection between the comparator and niraparib plus AAP via the network of available evidence; (2) availability of sufficient outcome data [i.e., to calculate the trial-specific relative treatment effect (RTE) and its standard error ([SE)] in the *BRCA*-positive population; (3) no within-study heterogeneity or bias that would influence the trial-specific RTEs within the *BRCA*-positive population; and (4) no between-study heterogeneity that would bias the RTEs estimated by the NMA within the *BRCA*-positive population [36]. The third criterion

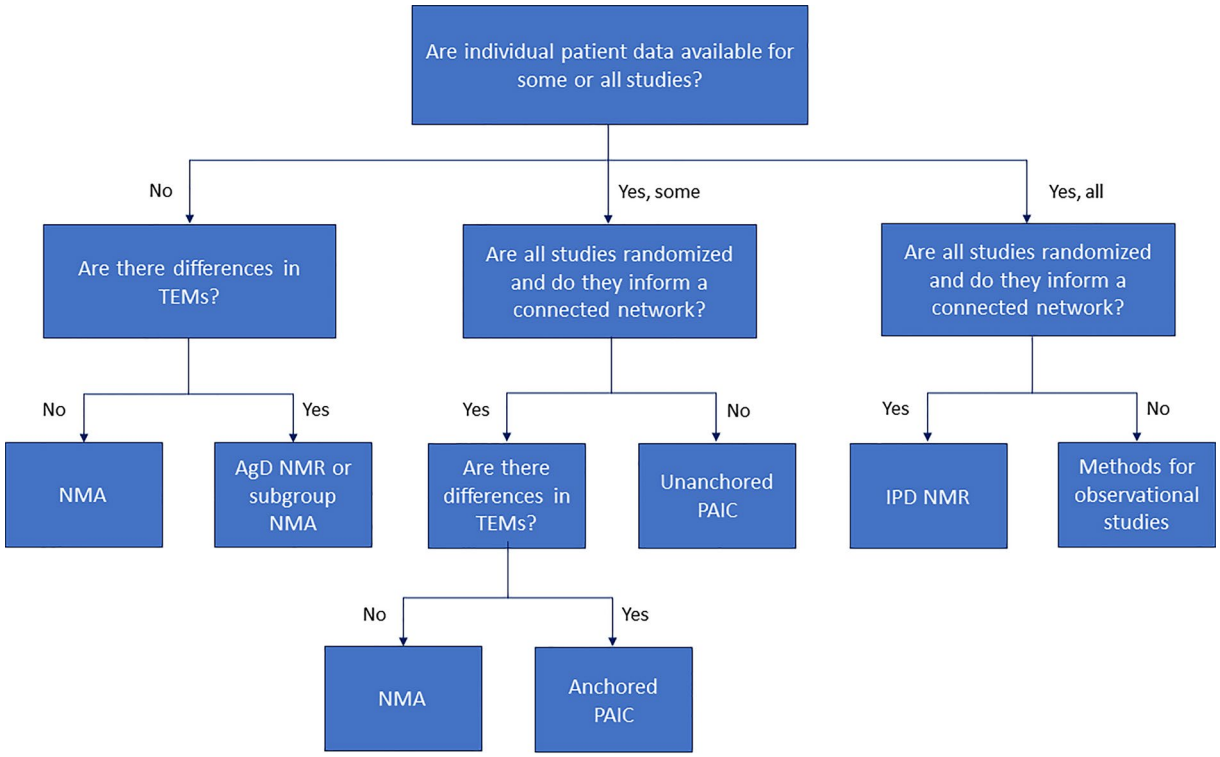

Fig. 1 Flowchart to aid ITC method selection, adapted from NICE DSU TSD18. *AgD* aggregate data, *DSU* decision support unit, *IPD* individual patient data, *ITC* indirect treatment comparison, *NICE* National Institute for Health and Care Excellence, *NMA* network meta-analysis, *NMR* network meta-regression, *PAIC* population-adjusted indirect comparison, *TEM* treatment effect modifier, *TSD* technical support document

assessed risk of bias due to the study conduct in each RCT (e.g., lack of blinding or poor concealment of randomization), imbalances in PVs across treatment groups within the *BRCA*-positive population, and the sensitivity of RTEs to data immaturity, treatment crossover, and small sample size. The fourth criterion was assessed by comparing relevant aspects of the population, outcome, and study characteristics of the RCTs, as well as the characteristics of common comparators to ensure they were sufficiently similar for NMA; differences in the patient population were acceptable if they related to factors that were not TEMs [32]. The ability to compare patient characteristics depended on the availability of baseline characteristics in the *BRCA*-positive subgroup. A full list of the criteria is provided in Table S2.

Assessing Feasibility of an Anchored PAIC

If an NMA was deemed infeasible, an anchored PAIC was subsequently considered. Criteria regarding no within-study heterogeneity or bias and the availability of sufficient outcome data are the same as those described above for the NMA feasibility assessment. For anchored PAICs, however, the connection must be via a common comparator rather than the network [niraparib plus AAP via AAP (i.e., the comparator must have been compared with AAP in its RCT)]. There should also be no between-study heterogeneity that will bias the indirect RTE between niraparib plus AAP and a relevant comparator within the *BRCA*-positive population that could not be adjusted for (Table S2) [36]. For anchored PAICs specifically, sufficient overlap must exist

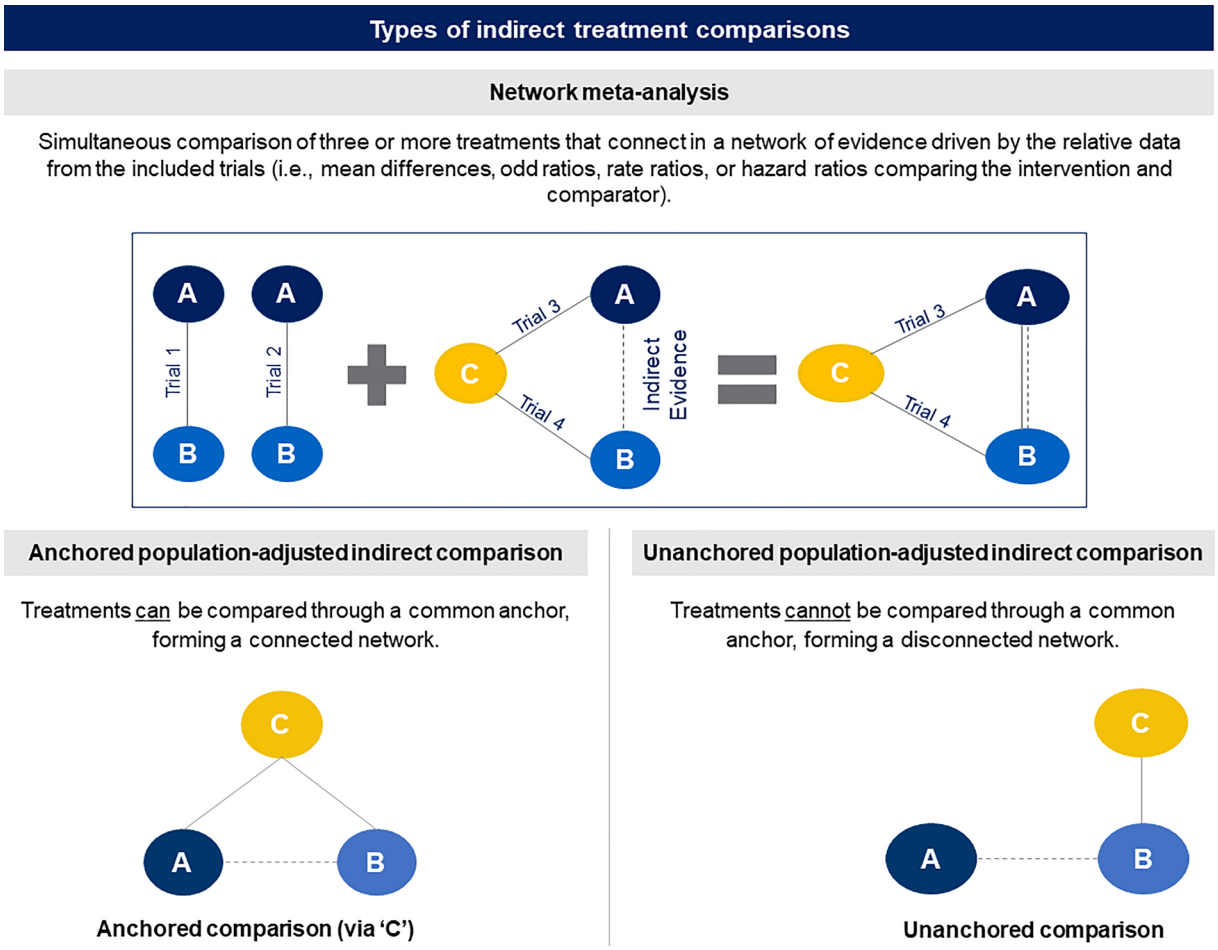

Fig. 2 Overview of indirect treatment comparison methods

in the distribution of the TEMs between MAGNITUDE and the comparator RCT to allow for population adjustment [32].

Assessing Feasibility of an Unanchored PAIC

Unanchored PAICs were only considered after NMA and anchored PAICs were ruled out. The appropriateness of an unanchored PAIC was assessed based on whether there was sufficient arm-level baseline characteristics and outcome data (i.e., absolute treatment effect and its SE). In addition, it was evaluated for any within-study or between-study heterogeneity or bias that would influence the absolute treatment effects (within-study) or the indirect RTE between niraparib plus AAP and a relevant comparator (between-study) within the *BRCA*-positive population that cannot be mitigated through PAIC methods (Table S2) [36]. Similar to the anchored PAIC approach, the overlap in both TEMs and PVs was analyzed to determine whether it was possible to use unanchored PAIC methods to adjust for population differences related to these factors. The frequency of assessment of progression outcomes was evaluated since any between-trial differences would lead to time-assessment bias [37].

Traditional PAICs such as matching-adjusted indirect comparison or simulated treatment comparison can only be applied to two studies at a time; therefore, the feasibility of PAICs for each pairwise comparison between niraparib plus AAP (via MAGNITUDE) and a relevant comparator was considered separately.

Data were not identifiable. Ethics committee approval was not required for this study. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Aggregate-level data recorded in MAGNITUDE's clinical study reports were fully accessible to the authors and the data presented in this paper were permitted for publication by the sponsor of the trial.

Aggregate-level data for all other trials were obtained from published articles identified in the publicly available MEDLINE®, MEDLINE® In-Process, and ClinicalTrials.gov databases, as well as the Embase, Cochrane Database of Systematic Reviews, and Cochrane Collaboration Central Register of Clinical Trials via Ovid.com databases which are available through a subscription. In addition, aggregate-level data were also sourced from reports published by health technology assessment agencies which are publicly available.

RESULTS

The database searches returned 4048 publications after de-duplication, with 636 included for full-text review, while 614 records were subsequently excluded, including articles on key trials investigating standard mCRPC therapies (e.g., AAP [38], enzalutamide [39], cabazitaxel [40], and docetaxel [40, 41]) which did not report outcomes in the *BRCA*-positive population. This resulted in 22 records being included in the SLR. Fourteen publications were identified through other sources (e.g., references of other SLRs, conference proceedings, sponsor-supplied documents on MAGNITUDE), of which four were excluded. Ultimately, 32 publications reporting on five unique RCTs—MAGNITUDE [4], PROfound [5], PROpel [8], TALAPRO-2 [21, 42], and TRITON-3 [22]—were selected for inclusion in the SLR. The literature attrition is shown in Figure S1.

TRITON-3 was not considered further since rucaparib is not approved for emerging therapy in this indication for most countries [20]. MAGNITUDE [4] prospectively screened for HRR mutations, then enrolled patients into three cohorts: (1) randomized HRR-positive; (2) randomized HRR-negative; and (3) HRR-positive who solely received niraparib plus AAP DAT. PROfound [5] also prospectively screened for HRR mutations and exclusively recruited patients with at least one qualifying HRR mutation; patients were randomized and divided into two cohorts: (1) *BRCA*1, *BRCA*2 or ATM mutations, and (2) all other patients. PROpel [8] recruited all-comer patients with unknown HRR mutation status into a single cohort; patients were retrospectively tested for HRR mutations after randomization. TALAPRO-2 [21, 42] also recruited patients from an all-comer population, but prospectively tested for HRR mutations and stratified patients by HRR mutation status during randomization; patients were then divided into two cohorts: (1) all-comers, and (2) patients who are HRR positive from Cohort 1 and additional patients who are HRR positive recruited after enrollment to Cohort 1 was complete. MAGNITUDE [4] was the only trial that stratified patients by *BRCA* mutation status during randomization (Table S3). All trials recorded information on patients who were *BRCA*-positive and reported some outcomes in this subgroup.

The baseline patient characteristics of these trials are presented in Table 1. Most patients were white and tended to be older, with a median age of at least 69 years in each study. At least half of the patients in Cohort 1 of MAGNITUDE were *BRCA*-positive [4], 41% of PROfound's patients were *BRCA*-positive [5], and 39% of patients in Cohort 2 of TALAPRO-2 were *BRCA*-positive [21, 42]. Only 11% of PROpel's population were *BRCA*-positive (n = 85) [8]. Most patients across the four trials had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1. All patients in MAGNITUDE [4], PROpel [8], and TALAPRO-2 [21, 42] were randomized to receive 1L mCRPC therapy, while most patients in PROfound [5] were randomized to receive second-line or later (2L+) treatment. In all trials, most patients had bone metastases. PROfound [5] and PROpel [8] had notably more patients with symptomatic pain [Brief Pain Inventory-Short Form (BPI-SF) item 3 ≥ 4), compared with MAGNITUDE [4].

Table 1 Baseline characteristics of MAGNITUDE, PROfound, PROpel, and TALAPRO-2

	MAGNITUDE				PROfound				PROpel				TALAPRO-2			
	Cohort 1 (HRR-positive)		Cohort 1 (BRCA-positive)		Overall population (HRR-positive)		BRCA-positive		Overall population		BRCA-positive		Cohort 1 (All-comer)		Cohort 2 (HRR-positive)	
	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP	OLA	AAP or ENZA	OLA	AAP or ENZA	OLA + AAP	PBO + AAP	OLA + AAP	PBO + AAP	TALA + ENZA	PBO + ENZA	TALA + ENZA	PBO + ENZA
Sample size																
	212	211	113	112	256	131	102	58	399	397	47	38	402	403	200	199
HRR-positive																
Yes	100%	100%	100%	100%	100%	100%	100%	100%	28%	29%	100%	100%	21%	21%	100%	100%
BRCA-positive																
Yes	53%	53%	100%	100%	40%	44%	100%	100%	12%	10%	100%	100%	7%	8%	36%	42%
Age (years)																
Median (mix, max)	69 (45, 100)	69 (43, 88)	67 (45, 100)	68 (43, 88)	69 (47, 91)	69 (49, 87)			69 (43, 91)	70 (46, 88)	67 (43, 83)	70 (46, 85)	71 (41, 90)	71 (36, 91)	70 (41, 90)	71 (44, 90)
Mean (SD)	69 (9)	69 (8)	68 (9)	68 (8)			67 (8)	67 (8)								
≥ 65	71%	71%	66%	70%	68%	74%					64%	71%				
Race																
White	76%	73%	69%	75%	64%	65%	66%	71%					60%	63%		
Black	2%	0%	3%	0%	3%	1%	2%	0%					3%	1%		
Asian	14%	19%	16%	18%	27%	27%	27%	17%					32%	30%		
Other	< 1%	< 1%	0%	0%	1%	1%	0%	2%					< 1%	< 1%		
Missing	8%	8%	12%	7%	6%	6%	6%	10%					< 1%	5%		
Time from initial diagnosis to randomization (months)																
Median (min, max)	29 (6, 319)	27 (6, 206)	24 (6, 220)	28 (6, 193)			23 (– 6, 119)	22 (1, 87)	34 (4, 288)	40 (1, 279)						
ECOG performance status																
0	61%	69%	61%	71%	51%	42%	50%	38%	72%	69%	77%	53%	64%	67%	64%	59%

Table 1 continued

	MAGNITUDE				PROfound				PROpel				TALAPRO-2			
	Cohort 1 (HRR-positive)		Cohort 1 (BRCA-positive)		Overall population (HRR-positive)		BRCA-positive		Overall population		BRCA-positive		Cohort 1 (All-comer)		Cohort 2 (HRR-positive)	
	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP	OLA	AAP or ENZA	OLA	AAP or ENZA	OLA + AAP	PBO + AAP	OLA + AAP	PBO + AAP	TALA + ENZA	PBO + ENZA	TALA + ENZA	PBO + ENZA
1	39%	31%	39%	29%	44%	54%	42%	57%	28%	31%	23%	47%	36%	33%	36%	41%
2					5%	3%	8%	5%								
Initial M stage at primary diagnosis																
M0	36%	46%	34%	50%									43%	46%	42%	42%
M1	60%	50%	62%	45%									51%	48%	58%	56%
Missing	4%	4%	4%	5%									5%	5%		
Metastatic disease at diagnosis																
Yes					26%	19%										
Missing					4%	5%										
Gleason score																
≥ 8	68%	68%	74%	64%	72%	73%	65%	64%	66%	65%	72%	66%	70%	70%	76%	72%
Missing			5%	5%	2%	0%	4%	2%	3%	1%	6%	3%	< 1%	2%	3%	2%
PSA (μg/L)																
Median (Q1, Q3)					68.2 (24.1, 294.4)	106.5 (37.2, 326.6)			17.9 (6.1, 67.0)	16.8 (6.3, 53.3)	29 (NR, NR)	22.5 (NR, NR)	18.2 (6.9, 59.4)	16.2 (6.4, 53.4)		
Median (mix, max)	21.4 (0.0, 4826.5)	17.4 (0.1, 4400.0)	18.7 (0.1, 2225.8)	14.1 (0.1, 4400.0)									18.2 (0.1, 2796.0)	16.2 (0.1, 2285.1)	19.6 (0.2, 3412.0)	18.0 (0.0, 1055.0)
Metastases at baseline																
Bone	86%	81%	88%	83%			89%	86%	88%	85%			87%	85%	88%	79%
Bone only	37%	40%	34%	41%	34%	29%	33%	26%			53%	53%	42%	38%	40%	39%
Visceral: lung or liver					27%	34%	29%	38%			11%	21%				
Liver	9%	6%	9%	6%					4%	5%			3%	4%	5%	3%

Table 1 continued

	MAGNITUDE				PROfound				PROpel				TALAPRO-2			
	Cohort 1 (HRR-positive)		Cohort 1 (BRCA-positive)		Overall population (HRR-positive)		BRCA-positive		Overall population		BRCA-positive		Cohort 1 (All-comer)		Cohort 2 (HRR-positive)	
	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP	OLA	AAP or ENZA	OLA	AAP or ENZA	OLA + AAP	PBO + AAP	OLA + AAP	PBO + AAP	TALA + ENZA	PBO + ENZA	TALA + ENZA	PBO + ENZA
Lung	13%	9%	11%	10%					10%	11%			11%	15%	12%	13%
Prior AAP use																
Yes																
Non-mCRPC setting	0%	0%	0%	0%					0%	0%	0%	0%	5%	6%	8%	8%
mCRPC setting	24%[a]	23%[a]	27%[a]	26%[a]					0%	0%	0%	0%	0%	0%	0%	0%
Previous novel AR targeted therapy																
Yes																
Non-mCRPC setting	4%	2%	5%	4%					< 1%	0%			< 1%[b]	< 1%[b]	< 1%[b]	< 1%[b]
mCRPC setting	0%	0%	0%	0%					0%	0%	0%	0%	0%	0%	0%	0%
Previously received AAP or enzalutamide																
Yes					100%[c]	100%[c]	98%[d]	100%								
Non-mCRPC setting					3%[c]											
mCRPC setting					> 96%[c]											
Previous taxane use																
Yes	19%	21%	23%	26%	66%	64%	71%	60%	24%	25%						
Non-mCRPC setting	19%	21%	23%	26%			11%	10%								
Docetaxel													21%	23%	29%	29%
At mHSPC									23%	22%	17%	26%				

Table 1 continued

	MAGNITUDE				PROfound				PROpel				TALAPRO-2			
	Cohort 1 (HRR-positive)		Cohort 1 (BRCA-positive)		Overall population (HRR-positive)		BRCA-positive		Overall population		BRCA-positive		Cohort 1 (All-comer)		Cohort 2 (HRR-positive)	
	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP	OLA	AAP or ENZA	OLA	AAP or ENZA	OLA + AAP	PBO + AAP	OLA + AAP	PBO + AAP	TALA + ENZA	PBO + ENZA	TALA + ENZA	PBO + ENZA
mCRPC setting	0%	0%	0%	0%			60%	50%	0%	0%	0%	0%	0%	0%	0%	0%
BPI-SF item 3																
0–3	93%	90%	95%	89%			62%	52%			66%	68%				
4–6											32%	26%				
> 4	7%	10%	5%	13%			34%	45%								
ALP (U/L)																
Median (Q1, Q3)									112.8 (81, 202.8)	109.8 (78, 201.0)						
Median (mix, max)	106.0 (36.0, 5234.0)	100.0 (47.0, 2651.0)	111.0 (36.0, 5234.0)	97.0 (47.0, 1892.0)												

AAP abiraterone acetate with prednisone, *ALP* alkaline phosphatase, *ARSi* androgen-receptor signaling inhibitor, *BPI-SF* Brief Pain Inventory-Short form, *ECOG* Eastern Cooperative Oncology Group, *ENZA* enzalutamide, *HRR* homologous recombination repair, *max* maximum, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *min* minimum, *NIRA* niraparib, *OLA* olaparib, *PBO* placebo, *PSA* prostate-specific antigen, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *TALA* talazoparib

[a]Prior AAP during mCRPC allowed up to 4 months prior to randomization while patients waited for genetic testing, provided they had no evidence of progression by PSA during screening

[b]Received orteronel

[c]Only 13 patients received new hormonal therapy prior to mCRPC only

[d]Data missing on two patients

Based on evidence reported from these four trials, factors that rendered an NMA or PAIC infeasible, or introduced large uncertainty as to the robustness of the NMA or PAIC, are noted below. The full comparability assessment, which details how these studies compared in terms of their study design, populations, intervention and comparators, and outcomes, is provided in the electronic supplementary material (Tables S1–S10).

Feasibility of Conducting an NMA

The network of evidence is presented in Fig. 3. Olaparib monotherapy and talazoparib plus enzalutamide did not connect to niraparib plus AAP, and thus an NMA involving these treatments was not possible (Fig. 2).

Data on all outcomes of interest [i.e., radiographic progression-free survival (rPFS) by blinded independent central review (BICR) and by investigator, overall survival (OS), time to second progression on next line (PFS2), time to prostate-specific antigen (PSA) progression, time to subsequent therapy, time to treatment discontinuation) were available in the *BRCA*-positive subgroup in MAGNITUDE. Outcome data were limited in the *BRCA*-positive population for all three comparator trials. PROfound [5] reported sufficient data for rPFS (by BICR) and OS; PROpel [8] reported sufficient data for rPFS (by BICR and investigator), OS, PFS2, time to PSA progression, and time to subsequent therapy; and TALAPRO-2 [21, 42] reported sufficient data for rPFS (by BICR) but data for OS were immature.

Although niraparib plus AAP was indirectly linked to olaparib plus AAP via the common AAP arms in PROpel [8] and MAGNITUDE [4], there was an imbalance of PVs in the *BRCA*-positive subgroup of PROpel, resulting from a lack of stratification by *BRCA* mutation status when

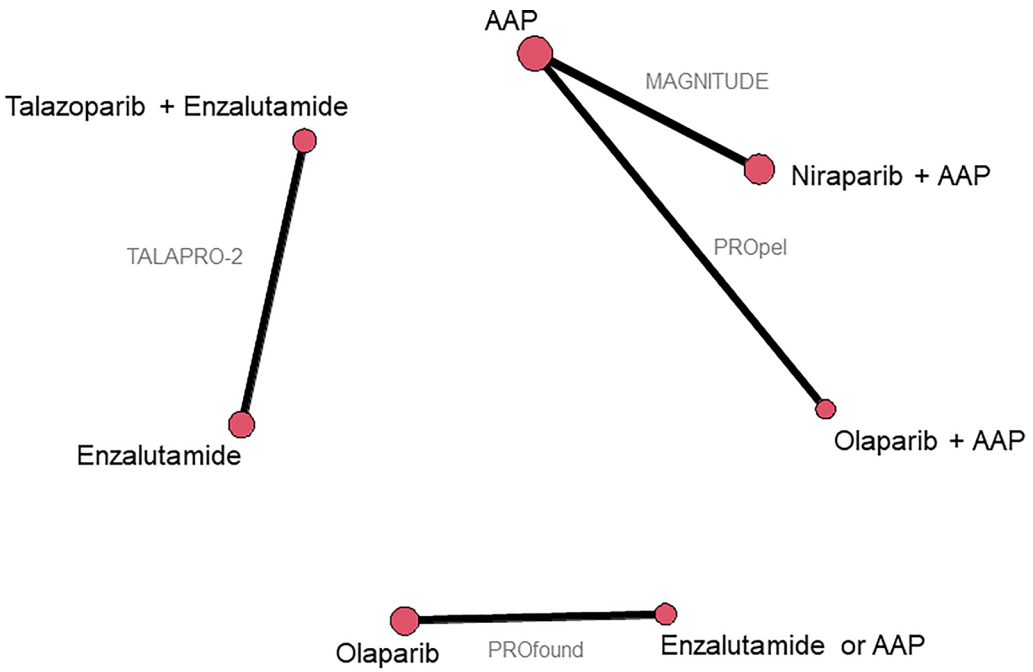

Fig. 3 Network diagram. *Node size* indicates the aggregated number of patients for each treatment across trials. *AAP* abiraterone acetate plus prednisone

randomizing patients, combined with a small sample size [8]. For example, 23% of patients in the olaparib plus AAP arm in PROpel had an ECOG PS score of 1 versus 47% in the AAP arm; 11% had visceral metastasis in the olaparib plus AAP arm versus 21% in the AAP arm (Table 1) [43]. Therefore, the RTEs in PROpel's *BRCA*-positive subgroup were likely biased in favor of the active olaparib plus AAP arm, which included patients with less severe baseline characteristics. In turn, these imbalances would bias the ITCs between niraparib plus AAP and olaparib plus AAP facilitated by NMA.

Similarly, PROfound [5] and TALAPRO-2 [21, 42] did not stratify by *BRCA* mutation status during randomization, and thus there was no guarantee that all PVs were balanced between the treatment groups within the *BRCA*-positive subgroups of these studies. Other within-study characteristics that would lead to bias in the trial-specific RTEs included treatment crossover in PROfound which was not adjusted for, and immature OS data in TALAPRO-2.

There was also heterogeneity in TEMs between the studies (e.g., treatment line, ECOG PS, Gleason score, BPI-SF item 3 score, presence of visceral metastases; Table S4), which would violate the validity of an NMA. The PROfound trial [5] included a mix of 1L and 2L+ patients, the majority of whom were 2L+ (> 96%), while MAGNITUDE [4] patients were strictly 1L. In addition, there were fewer patients with an ECOG PS score of 0, fewer with a Gleason score ≥ 8, and more patients with a BPI-SF item 3 score ≥ 4 in PROfound compared with MAGNITUDE. In PROpel [8], only limited baseline characteristics were available in the *BRCA*-positive subgroup, and, of the characteristics reported, more patients had an ECOG PS score of 0, bone-only metastases, and a BPI-SF item 3 score ≥ 4 compared with MAGNITUDE. Baseline characteristics in the *BRCA*-positive subgroup in TALAPRO-2 [21, 42] were not available, and thus the distribution of TEMs between TALAPRO-2 and MAGNITUDE could not be compared within the BRCA-positive subgroups.

Several factors ultimately prevented a valid NMA between niraparib plus AAP and other PARPi treatments within the target population (Fig. 4), including the disconnected networks, known cross-trial population differences, and within-study bias in the PROpel's *BRCA*-positive subgroup. Limited outcome data in this subgroup also prevented NMAs for all efficacy outcomes of interest.

Feasibility of Conducting PAICs

Since olaparib monotherapy and talazoparib plus enzalutamide were not connected to niraparib plus AAP via a common comparator, anchored PAICs were not possible (Fig. 2). Additionally, as was the case in the NMA, anchored PAICs between niraparib plus AAP and olaparib plus AAP were not appropriate due to imbalances in PVs within the *BRCA*-positive subgroup of PROpel [8]. Other within-study limitations that would bias the trial-specific RTEs, as noted above in the NMA feasibility assessment, also applied to anchored PAICs. Therefore, the possibility of using unanchored PAIC was explored to determine if this method would facilitate valid and robust ITCs in the target population. The considerations are summarized in Fig. 5.

Niraparib Plus AAP (MAGNITUDE) vs. Olaparib Monotherapy (PROfound)

While PROfound reported sufficient arm-level baseline characteristics [44] and data for some outcomes of interest in the *BRCA*-positive subgroup, > 96% of patients were 2L+ [5]. MAGNITUDE [4] only included 1L patients. The lack of overlap in the distribution of this TEM (i.e., treatment line) made it impossible to match or simulate MAGNITUDE patients to a 2L+ population via PAIC; thus, an unanchored PAIC was deemed inappropriate.

Niraparib Plus AAP (MAGNITUDE) vs. Olaparib Plus AAP (PROpel)

PROpel [8], to date, has reported a limited set of arm-level baseline characteristics in the *BRCA*-positive subgroup: age, ECOG PS score, Gleason score, baseline PSA, prior docetaxel at metastatic hormone-sensitive PC, bone metastases, visceral metastases, and baseline

Fig. 4 Checklist of criteria required for an NMA niraparib plus AAP (MAGNITUDE). *AAP* abiraterone acetate with prednisone, *NMA* network meta-analysis

BPI-SF item 3 score [43]. Although it is possible to adjust for these PVs or TEMs, other important PVs cannot be adjusted for (e.g., baseline alkaline phosphatase, baseline lactate dehydrogenase, number of bone lesions, and metastatic stage at diagnosis). Although sufficient arm-level outcome data in the *BRCA*-positive subgroup were reported in PROpel for rPFS by BICR, rPFS by investigator, and OS, the small number of patients receiving olaparib plus AAP among the *BRCA*-positive group ($n = 47$) would make the point estimate of any comparison very sensitive to the (low) number of events within this subgroup. Additionally, PROpel excluded use of AAP in mCRPC prior to randomization. Given this exclusion criteria, an unanchored PAIC would exclude patients with prior AAP from MAGNITUDE, reducing the number of patients who are *BRCA*-positive receiving niraparib plus AAP from 113 to 83. Although an unanchored PAIC was deemed possible for this comparison for a small number of outcomes, its robustness was unclear, based on published evidence to date due to the aforementioned reasons.

Niraparib Plus AAP (MAGNITUDE) vs. Talazoparib Plus Enzalutamide (TALAPRO-2)

TALAPRO-2 [21, 42] has not yet reported any baseline characteristics among the patients who are *BRCA*-positive, which prevents adjustment for differences in PVs in this subgroup. In addition, sufficient arm-level outcome data (e.g., Kaplan–Meier curve or median survival and SE for the talazoparib plus enzalutamide arm) have not been published and OS data are immature. Therefore, an unanchored PAIC was not

Fig. 5 Challenges of conducting PAIC with niraparib plus AAP (MAGNITUDE). *AAP* abiraterone acetate with prednisone, *PAIC* population-adjusted indirect comparison, *PV* prognostic variables, *TEM* treatment effect modifiers

deemed possible given current published data. TALAPRO-2 did not permit prior ARSi use after mCRPC diagnosis, so patients with prior AAP use after mCRPC diagnosis in MAGNITUDE would need to be excluded, reducing the number of patients available for the PAIC. Although PAICs could be conducted once arm-level baseline characteristics and outcome data become available, there may not be a sufficient sample size to produce a robust comparison.

DISCUSSION

PARPis in combination with ARSis are the most effective treatments for patients with 1L mCRPC harboring *BRCA* mutations [4, 8, 21], yet no head-to-head RCTs (the preferred evidence source given their high internal and external validity [45]) exist to estimate the comparative efficacy between niraparib plus AAP (evaluated in MAGNITUDE [4]) and other PARPis, either as standalone therapies or combined with ARSis. Recent trials have investigated other PARPi treatments in the population of interest (e.g., PROfound [5], PROpel [8], and TALAPRO-2 [21, 42]), but all were designed to address different unmet needs.

In the absence of RCTs, this ITC feasibility assessment explored whether an NMA or PAIC between niraparib plus AAP and PARPis was methodologically plausible. Several factors determine feasibility, including the ability to connect the network, the availability of baseline characteristics (and outcome data) in the

BRCA-positive subgroup, imbalances in baseline characteristics or other factors that bias the RTE estimates in each trial's *BRCA*-positive subgroup, and between-study heterogeneity in terms of their population, outcomes, and study characteristics, all which need to be met to conduct a robust analysis [32, 36, 46].

The current assessment highlighted numerous challenges concerning network connectivity, differences in study design, population heterogeneity, and data availability. The lack of a connected network for studies reporting outcomes on the *BRCA*-positive population, along with biased relative effects within PROpel [8], rendered NMAs infeasible. Similarly, the lack of a common comparator among MAGNITUDE, PROfound, and TALAPRO-2, as well as the biased relative effects within PROpel, meant anchored PAICs were impossible or inappropriate. Unanchored PAICs between niraparib plus AAP and olaparib monotherapy, olaparib plus AAP, and talazoparib plus enzalutamide are the only potentially valid method to facilitate ITCs; however, this would require sufficient arm-level baseline characteristics (i.e., PVs that need to be adjusted for) and outcome data (e.g., Kaplan–Meier curves or median survival) in the *BRCA*-positive subgroup, as well as sufficient population overlap to adjust for differences in patient characteristics. Ultimately, this feasibility assessment identified many potential limitations associated with conducting these PAICs: MAGNITUDE [4] and PROfound [5] differed in populations in terms of line of therapy; small sample size and limited baseline characteristics were reported in the *BRCA* population in PROpel [8]; and there was a lack of arm-level baseline characteristics and efficacy outcome data reported in the *BRCA* population by TALAPRO-2 [21, 42]. Rucaparib was not considered in this feasibility assessment since it is not an approved or emerging 1L treatment for *BRCA*-positive mCRPC in most countries. Nonetheless, a comparison between niraparib plus AAP and rucaparib would be inappropriate since most patients in TRITON-3 [22] were previously treated with ARSis (no outcomes were reported for patients who were not previously treated).

Considering the differences in populations and limited data on PARPi therapies within the *BRCA*-positive subgroup, ITCs using current evidence from the PARPi RCTs would result in low internal validity and a high risk of bias, producing unreliable evidence to inform clinical and reimbursement decision-making. In the absence of head-to-head randomized evidence comparing PARPi treatment options in mCRPC, clinical experience and real-world evidence (RWE) can provide valuable insights into outcomes from the perspective of patients with *BRCA*-positive mCRPC. Healthcare decision-makers have recognized the multidimensional nature of determining the value of a new treatment [47], and both clinical experience and RWE play an integral role in examining what matters most to patients and caregivers. Future studies on PARPi treatments in the *BRCA*-positive population should aim to balance sufficient efficacy and good tolerability by prioritizing outcomes such as treatment duration or time to treatment discontinuation. In addition, health-related quality-of-life measures can capture the benefits of a novel treatment from not only the patient perspective but also from that of caregivers.

In terms of clinical decision-making in the context of 1L mCRPC, the new PARPi treatment options provide strong evidence of clear benefits for the *BRCA*-positive population over current ARSi options [4, 8, 12, 21]. Physicians should determine a patient's *BRCA* mutation status early in metastatic disease prior to the diagnosis of CRPC to hasten patient access to PARPis, which are more effective than ARSi alone [4, 8, 12, 21]. The choice among PARPis based on efficacy outcomes, however, is less clear, as there is no head-to-head evidence nor any way of conducting robust ITCs to facilitate comparisons. This assessment highlights the need for physicians to consider the patient's characteristics and treatment toxicity profile when selecting an appropriate treatment in the absence of methodologically sound treatment comparisons.

According to the recent guidelines on prostate cancer, PARPi in combination with ARSi are strongly recommended to patients in 1L mCRPC with relevant DNA repair gene variants, which are, for BRCA mutations, abiraterone in combination with niraparib and for HRR or BRCA mutations, abiraterone in combination with olaparib or enzalutamide in combination with talazoparib [48]. Considering that the PARPi combination

regimens have all received global regulatory approvals, future studies explicitly designed to evaluate comparative efficacy and safety would inform their relative benefits in clinical practice. Clinical insights and patient experience should be gathered to highlight the treatments that maximize time to disease progression and to minimize adverse events, so that patient quality of life is maintained for as long as possible.

LIMITATIONS

This study was limited by the availability of individual patient data (IPD) and aggregate level data among patients with BRCA mutations. Network meta-regression with full disclosure of IPD across trials may have increased the feasibility of robust ITCs in this population; however, IPD is rarely shared across manufacturers. As IPD were only available for MAGNITUDE in this study, and anchored ITCs were not possible nor valid with aggregate-level data for the other trials, unanchored PAICs were the only methodologically robust option available. Feasibility of PAIC is also limited by published aggregate-level data among patients with BRCA mutations at the time of writing.

CONCLUSION

The RCT evidence network does not permit robust comparisons between niraparib plus AAP and other PARPi regimens for patients with 1L *BRCA*-positive mCRPC. Given the limitations of any ITC approach with current RCT evidence, clinical and reimbursement decision-makers should interpret any results in this context. Data from RWE studies combined with clinical experience could guide the decision-making process as clinicians and patients weigh the benefits and risks associated with each treatment.

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Declarations

Conflict of Interest. Maria De Santis: received honoraria for consultancy and advisory boards by AAA, Amgen, Astellas, AstraZeneca, Basilea, Bayer, Bioclin, BMS, EISAI, Ferring, Immunomedics/Gilead, Ipsen, Janssen, MSD, Merck, Novartis, Pfizer, Orion, Roche, Sandoz, Sanofi, SeaGen Sara Martínez Breijo: provided scientific advice to Janssen, Bayer, Astellas; participated in medical meetings organized by Astellas, Astra-Zeneca, Bayer, Ipsen, Janssen, Opko, Palex and Sanofi; received payments for presentations from Astellas, Amgen, Astra-Zeneca, Bayer, Ipsen, Janssen, and Sanofi. Paul Robinson, Camille Capone, Katie Pascoe, Suzy Van Sanden, Mahmoud Hashim, and Marco Trevisan are employees of Janssen; Caitlin Daly, Friso Reitsma, Sophie van Beekhuizen, Haoyao Ruan, and Bart Heeg are employees of Cytel which was commissioned by Janssen for the study. Current affiliations: Haoyao Ruan: PhD student in the

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Ethical Approval. Data were not identifiable. Ethics committee approval was not required for this study. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Aggregate-level data recorded in MAGNITUDE's clinical study reports were fully accessible to the authors and the data presented in this paper were permitted for publication by the sponsor of the trial. Aggregate-level data for all other trials were obtained from published articles identified in the publicly available MEDLINE®, MEDLINE® In-Process, and ClinicalTrials.gov databases, as well as the Embase, Cochrane Database of Systematic Reviews, and Cochrane Collaboration Central Register of Clinical Trials via Ovid.com databases which are available through a subscription. In addition, aggregate-level data were also sourced from reports published by health technology assessment agencies which are publicly available.

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