A systematic literature review (SLR) and indirect treatment comparison (ITC) feasibility assessment (FA) in homologous recombination repair (HRR)-deficient metastatic castration-sensitive prostate cancer (mCSPC)

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Objective

To conduct a SLR and FA to evaluate the appropriateness of ITCs for estimating the relative efficacy of treatments in patients with HRR-deficient mCSPC.

Conclusions

- Unanchored population-adjusted ITCs between TALAPRO-3 and AMPLITUDE were considered feasible.
- Differences in HRR gene eligibility, performance status, and prior treatment exposure should be adjusted for where possible.
- Comparisons with other standard-of-care regimens may require real-world external controls.

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Background

- Despite advances in systemic therapy, patients with HRR-deficient mCSPC remain at increased risk of poor clinical outcomes, highlighting the need for effective targeted treatment strategies such as poly (ADP-ribose) polymerase inhibitors (PARPis).[1-5]
- Clinical evidence evaluating treatment outcomes in patients with HRR-deficient mCSPC is limited, with few direct comparisons with approved therapies.
- ITCs may provide estimates of comparative treatment effects when head-to-head evidence is unavailable.
- Robust assessment of heterogeneity is required to support valid and transparent ITC findings.[6]
- Therefore, an SLR and FA were conducted to determine the appropriateness of ITCs in HRR-deficient mCSPC.

Materials and Methods

SYSTEMATIC LITERATURE REVIEW

- An SLR was conducted to identify evidence from inception through January 2026
  - Methods aligned with guidance from Cochrane Handbook and PRISMA statement.[7,8,9]
- Sources included MEDLINE®, Embase, and Cochrane (searched via Ovid®), supplemented by key grey literature sources.
- Randomized controlled trials (RCTs) (not restricted by phase) and single-arm trials (excluding phase 1) of available first-line therapies for mCSPC, regardless of HRR-deficient status, were included in the SLR (see **Table 1** for eligibility criteria).

Table 1: PICOS Criteria for Clinical SLR

	Inclusion Criteria
Population	• Adults with mCSPC receiving first-line systemic therapy*
Intervention(s)	• Available or investigational systemic therapies for mCSPC, including PARP inhibitor-, ARPI-, chemotherapy-, AKT inhibitor-, and radioligand-based regimens
Comparator(s)	• Placebo • Standard of care/usual care control/best supportive care • Any alternative active intervention of interest
Outcome(s)	• Efficacy, safety, health-related quality of life, and patient-reported outcomes
Study Design	• RCTs of any phase and nonrandomized clinical trials, excluding phase 1 studies

*Studies with mixed populations were eligible if ≥80% of participants met the population criteria or if results were reported separately for the population of interest.

ITC FEASIBILITY ASSESSMENT

- An FA was conducted to determine whether trials identified in the SLR were sufficiently similar for inclusion in a valid ITC.
- Several ITC approaches were evaluated, including network meta-analyses (NMAs) and population-adjusted methods (matching-adjusted indirect comparisons [MAICs] and simulated treatment comparisons [STCs]).
- Trial heterogeneity was assessed based on study design, baseline characteristics, and outcome availability and definitions.
- Only trials conducted in HRR-deficient populations were considered suitable for inclusion.
  - Comparisons with trials enrolling HRR-nondeficient or unconfirmed HRR populations were excluded based on clinical expert feedback regarding population heterogeneity.
- Outcomes of interest were investigator-assessed radiographic progression-free survival (rPFS) and overall survival (OS).

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Abbreviations: ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; ECOG = Eastern Cooperative Oncology Group; FA = feasibility assessment; HRR = homologous recombination repair; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; mCSPC = metastatic castration-sensitive prostate cancer; NMA = network meta-analysis; OS = overall survival; PARPi = poly ADP-ribose polymerase inhibitor; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PS = performance status; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; SLR = systematic literature review; STC = simulated treatment comparison.

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Results

SLR RESULTS

- In total, 26 trials (19 RCTs and 7 single-arm trials) were identified in the SLR; however, 22 trials did not investigate confirmed HRR-deficient populations. The remaining four clinical trials (two RCTs and two single-arm) enrolled confirmed HRR-deficient populations.

ITC FEASIBILITY ASSESSMENT

- ITC feasibility was assessed in a stepwise manner for each ITC method, as presented in **Figure 1**.
- The FA included the four trials conducted in confirmed HRR-deficient populations (**Table 2**).

Figure 1: Flow Diagram of the ITC Feasibility Assessment for (A) NMAs; and (B) MAICs and STCs

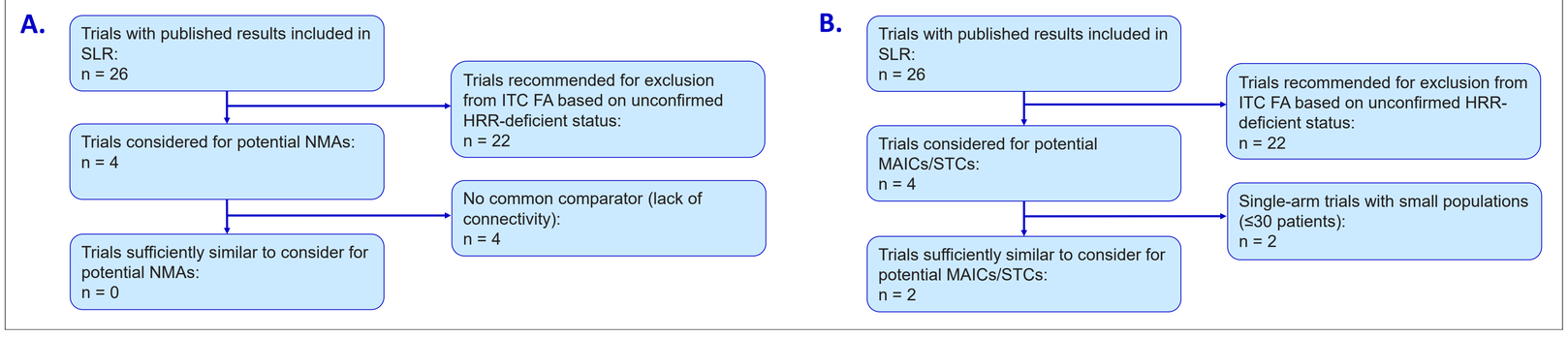


Table 2: Study Design of Identified HRR-Deficient Trials

Study Name; NCT	Study Design	Intervention	Comparator	N enrolled	Reported Outcomes of Interest
TALAPRO-3 NCT04821622	Phase 3 double-blind RCT	Talazoparib + enzalutamide	Placebo + enzalutamide	599	rPFS (investigator), OS
AMPLITUDE NCT04497844	Phase 3 double-blind RCT	Niraparib + abiraterone + prednisone	Placebo + abiraterone + prednisone	696	rPFS (investigator), OS
PROact NCT05167175	Phase 2 open label single-arm trial	Olaparib + abiraterone + prednisone	NA	30	rPFS (investigator)
TRIUMPH NCT03413995	Phase 2 open label single-arm trial	Rucaparib	NA	12	rPFS (investigator)

NMA FEASIBILITY ASSESSMENT

- No common comparator was identified among the HRR-deficient trials included in the FA (**Table 2**); therefore, the evidence network lacked the connectivity required for an NMA, rendering this approach infeasible (**Figure 1A**).

POPULATION-ADJUSTED ITC FEASIBILITY ASSESSMENT (MAICs/STCs)

Study Design:

- PROact and TRIUMPH were single-arm trials with small sample sizes (≤30 patients) and did not report all outcomes of interest (OS) (**Figure 1B; Table 2**); therefore, they were excluded from further ITC FA sections.
- TALAPRO-3 and AMPLITUDE were multicenter, double-blind, phase 3 RCTs that reported all outcomes of interest and were retained (**Table 2**).

Eligibility Criteria:

- TALAPRO-3 and AMPLITUDE enrolled adults with confirmed HRR-deficient mCSPC, but differed in eligibility related to HRR genes, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and prior treatment (**Table 3**).
  - TALAPRO-3 included a broader HRR12 gene panel, whereas AMPLITUDE limited enrollment to a distinct set of HRR genes.
  - ECOG PS criteria differed between studies (TALAPRO-3: ≤1; AMPLITUDE: ≤2).
  - Prior docetaxel use was prohibited in TALAPRO-3 but permitted in AMPLITUDE (≤6 cycles completed within 3 months of randomization).
  - Prior androgen receptor pathway inhibitor (ARPI) exposure also differed; TALAPRO-3 permitted ≤3 months of androgen deprivation therapy (ADT) with or without an approved ARPI, whereas AMPLITUDE permitted ≤45 days of abiraterone plus prednisone only.

Baseline characteristics:

- Reported baseline characteristics were generally similar between TALAPRO-3 and AMPLITUDE (data not shown).

Connectivity:

- TALAPRO-3 and AMPLITUDE did not share a common comparator; therefore, future MAICs/STCs would be unanchored.

Table 3: Eligibility Criteria of Identified Studies

Study Name; NCT	Age/Status	Disease-Related	Prior Treatment	HRR mutations included
TALAPRO-3 NCT04821622	• ≥18 years • ECOG ≤1	• Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation • Alterations in one or more HRR gene • Metastatic disease in bone documented on bone scan or in soft tissue	• Prior use of docetaxel prohibited • ≤3 months of ADT (with or without approved ARPIs) permitted	ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C
AMPLITUDE NCT04497844	• ≥18 years • ECOG ≤ 2	• Pathological diagnosis of prostate adenocarcinoma • Alterations in one or more HRR gene • Metastatic disease as documented by conventional imaging or bone scan	• Prior use docetaxel permitted • ≤45 days abiraterone + prednisone permitted	BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L

FINAL RESULTS/RECOMMENDATIONS

- NMAs are not recommended due to a lack of connectivity across confirmed HRR-deficient trials.
- MAICs/STCs with single-arm trials (PROact and TRIUMPH) were not recommended due to small sample sizes (≤30 patients), which would increase uncertainty of estimates, and lack of OS reporting (**Figure 1B; Table 2**).
- MAICs/STCs between TALAPRO-3 and AMPLITUDE were feasible and recommended.
  - Analyses would be unanchored due to the absence of a common comparator.
  - Differences in ECOG PS, HRR gene eligibility, and prior treatment exposure should be adjusted for where possible in future MAICs/STCs.
- External control arm analyses using real-world data may provide the necessary evidence for comparative effectiveness of PARP inhibitor-containing treatment to standard of care in HRR-deficient populations.
  - A formal FA is required to evaluate sample size adequacy and potential for generating reliable comparative effectiveness estimates.