Abstract #3389 : Systemic Therapies in Docetaxel (DTX)-Naïve, Biomarker-Unselected Metastatic Castration-Resistant Prostate Cancer (mCRPC) post Androgen Receptor Pathway Inhibitor (ARPI)/Androgen Deprivation Therapy (ADT): A Systematic Literature Review (SLR) & Indirect Treatment Comparison (ITC)

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Background

- Metastatic castration-resistant prostate cancer (mCRPC; now also referred to as mAPMR under PCWG4) remains a challenging disease setting in which treatment sequencing after progression on androgen deprivation therapy (ADT) and/or androgen receptor pathway inhibitor (ARPI) therapy is not well established.
- The National Comprehensive Cancer Network (NCCN) endorses six systemic therapies for docetaxel-naïve, biomarker-unselected mCRPC after ARPI progression: docetaxel; cabazitaxel (docetaxel-ineligible or -intolerant patients); radium-223 (symptomatic bone-predominant metastases); sipuleucel-T (asymptomatic patients); ^{177}Lu-PSMA-617 (lutetium; PSMA-positive disease); and cabazitaxel plus carboplatin (aggressive variant).[1] Direct comparative evidence among these options, however, remains limited.
- In our review, "biomarker-unselected" refers to the absence of selection based on predictive genomic biomarkers; studies requiring PSMA imaging for patient selection, such as those evaluating ^{177}Lu-PSMA-617, were eligible for inclusion.
- Although docetaxel is the only NCCN Category 1 option, many patients cannot receive or tolerate it due to comorbidities, age, or toxicity concerns.[1-3] Cabazitaxel is recommended for docetaxel-ineligible/intolerant patients; in FIRSTANA, cabazitaxel 20 mg/m^2 (C20) showed no significant efficacy differences versus docetaxel, with better tolerability.[4]
- Although the efficacy and safety of docetaxel have been extensively characterized, less is known about the relative positioning of C20 compared with other contemporary systemic treatment options available for docetaxel-ineligible or docetaxel-intolerant patients, representing an important unresolved clinical question.
- As head-to-head comparative evidence remains scarce, indirect comparative approaches may provide clinically meaningful insight regarding the relative efficacy and safety of available therapies in this setting.

Objectives

- To evaluate six NCCN-endorsed systemic therapies for docetaxel-naïve, biomarker-unselected mCRPC after progression on prior ADT and/or ARPI via a systematic literature review (SLR) of randomized controlled trials (RCTs). Additionally, to quantify the relative efficacy and safety of cabazitaxel 20 mg/m^2 (C20) vs. other NCCN-endorsed systemic therapies in this setting via an indirect treatment comparison (ITC).

Methods

Systematic Literature Review (SLR)

- An SLR was conducted by searching MEDLINE®, Embase, and CENTRAL to identify RCTs published between January 1, 2011, and November 5, 2025.
- Grey literature searches included:
  - Conference proceedings from American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), NCCN, European Society for Medical Oncology (ESMO), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (2022-2025).
  - Clinical trial registries [United States (US) and European Union (EU)].
- Eligible RCTs enrolled adults with docetaxel-naïve biomarker-unselected mCRPC following prior ADT and/or ARPI and reported efficacy or safety outcomes.
- Outcomes included overall survival (OS), progression-free survival (PFS), prostate-specific antigen (PSA) response, objective response rate (ORR), adverse events (AEs), serious adverse events (SAEs), and treatment discontinuation.

Indirect Treatment Comparison (ITC)

- Bucher ITC methodology was used to estimate comparative efficacy and safety while preserving within-trial randomization.[5] A feasibility assessment was conducted to identify a connected evidence network and evaluate study comparability prior to the ITC. The predefined SLR protocol was designed to identify evidence across all six NCCN-endorsed therapies and determine which could form a connected evidence network. The identified trials produced a connected network through docetaxel as the common comparator, enabling indirect comparisons of C20 with ^{177}Lu-PSMA-617 and radium-223 plus docetaxel; these were the only comparisons supported by the available evidence.
- Time-to-event outcomes were analyzed using hazard ratios (HRs) and dichotomous outcomes were analyzed using risk ratios (RRs). A continuity correction of 0.5 was applied to the latter when no events were observed in an arm of a study.
- Analyses were performed on log transformed HRs and RRs using R version 4.4.0. For comparisons informed by more than two studies, random-effects meta-analyses (MAs) were performed using the 'metafor' package[6] (restricted maximum likelihood estimator for tau) to account for between-study heterogeneity. Statistical significance was defined as $p < 0.05$.
- Sensitivity analyses were performed excluding one trial (PR.21)[7] which, relative to the other studies, reported lower baseline PSA levels and lower rates of PSA and tumor response in the docetaxel control arm.

Results

Study Selection and Evidence Base

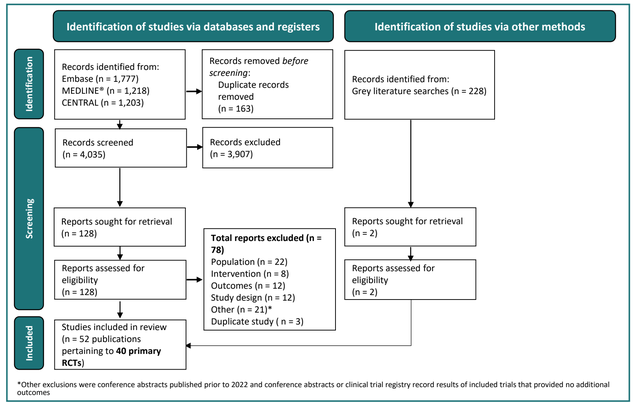
- The SLR identified 4,426 records, resulting in the inclusion of 52 publications representing 40 unique RCTs (**Figure 1**).
- Following feasibility assessment, 36 trials were excluded because they either did not contribute to the connected evidence network, evaluated cabazitaxel 25 mg/m^2, or did not inform a comparison of interest (**Figure 2**).

SLR Findings

- Docetaxel was evaluated in 36 RCTs and demonstrated median OS of approximately 17-21 months across studies.
- Three cabazitaxel RCTs showed no clinically meaningful efficacy differences versus docetaxel. In FIRSTANA, C20 reduced grade ≥3 AEs (41% vs. 46%) and discontinuations due to toxicity (25.2% vs. 34.4%); rates of peripheral neuropathy and edema were nearly half vs. docetaxel.
- Three ^{177}Lu-PSMA-617 RCTs demonstrated improved rPFS (vs. ARPI switch) and PSA response (vs. ARPI switch and docetaxel).
- Two radium-223 RCTs demonstrated OS benefits vs. placebo; one radium-223 plus docetaxel RCT showed a numerically higher PSA response vs. docetaxel alone.
- The only sipuleucel-T RCT showed improved PFS and higher PSA response with sipuleucel-T + radium-223 vs. sipuleucel-T alone.
- No RCTs assessing cabazitaxel plus carboplatin were identified.
- Across the overall evidence base, C20 showed no significant efficacy differences and a more favorable tolerability profile versus higher-dose taxanes, supporting its role as an alternative taxane option in selected patients.
- Despite identification of 40 RCTs, only four studies formed a connected evidence network, highlighting the limited comparative evidence available among NCCN-endorsed therapies in this setting.

Results (contd.)

Figure 1: PRISMA Diagram



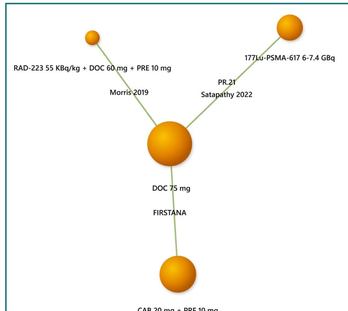
*Other exclusions were conference abstracts published prior to 2022 and conference abstracts or clinical trial registry record results of included trials that provided no additional outcomes

ITC Findings

Study Characteristics

- The characteristics of RCTs included in the ITC are presented in **Table 1**.

Figure 2: Network Diagram for the ITC



- 40 RCTs were identified in the SLR and assessed for network connectivity.
- Out of 40 RCTs, 36 were excluded:
  - 31 RCTs were not connected to the treatment network required for indirect comparisons
  - 2 cabazitaxel 25 mg/m^2 RCTs were excluded (CABADOC and TAXYNERGY) to focus on the approved cabazitaxel 20 mg/m^2 dose
  - 3 additional RCTs were excluded because they did not inform a comparison of interest (PSMAfore, Marshall et al. (2021), ALSYMPCA).
- 4 RCTs were retained for the ITC: FIRSTANA,[4] PR.21,[7] Satapathy et al. (2022),[8] and Morris et al. (2019).[9] These RCTs formed the final connected evidence network supporting indirect comparisons between cabazitaxel 20 mg/m^2, ^{177}Lu-PSMA-617, and radium-223 plus docetaxel.

*177Lu-PSMA-617 – lutetium radioligand therapy; CAB – cabazitaxel; DOC – docetaxel; GBq – gigabecquerel; KBq – kilobecquerel; PRE – prednisone/prednisolone; RAD – radium

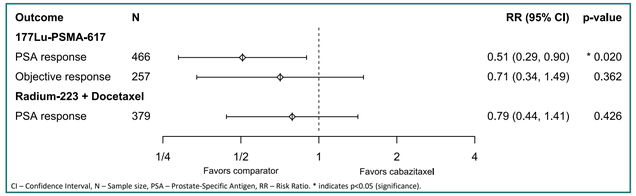
Table 1: Characteristics of RCTs Included in the ITC

Trial	Clinical Trial #	Phase	Region and Setting	Sample Size	Interventions
FIRSTANA[4]	NCT01308567	III	Global, multicenter	1,168	Patients received C20, C25, or D75 Q3W with daily 10 mg prednisone until disease progression, unacceptable toxicity, or patient decision.
Satapathy et al. (2022)[8]	CTRI/2019/12/02228	II	India, single-center	40	Patients received D75 Q3W with 10 mg daily prednisone for up to 10 cycles, or ^{177}Lu-PSMA-617 6.0–7.4 GBq/cycle Q8W for up to four cycles.
PR.21[7]	NCT04663997	II	Canada, multicenter	199	Patients received D75 Q3W for 12 cycles (concomitant prednisone use was not explicitly reported) or ^{177}Lu-PSMA-617 7.4 GBq/cycle Q6W for six cycles.
Morris et al. (2019)[9]	N/A	II	Europe and North America, multicenter	53	Patients received D75 Q3W with 10 mg daily prednisone or radium-223 55 kBq/kg with D60 Q3W and 10 mg daily prednisone for up to 30 weeks or until significant toxicity.

C20 – Cabazitaxel 20 mg/m^2, C25 – Cabazitaxel 25 mg/m^2, D75 – Docetaxel 75 mg/m^2, NCCN – National Comprehensive Cancer Network, NCT – National Clinical Trial, Q3W – Every three weeks, Q8W – Every eight weeks.

ITC – Efficacy Findings

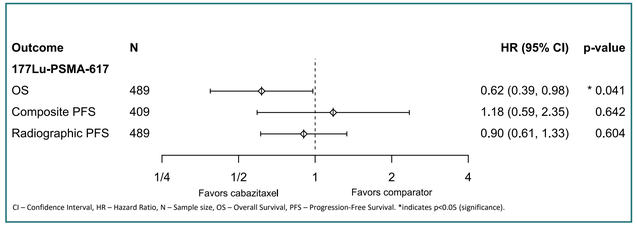
Figure 3: ITC Results for PSA and Objective Tumor Responses



CI – Confidence Interval, N – Sample size, PSA – Prostate-Specific Antigen, RR – Risk Ratio. * indicates p<0.05 (significance).

- Compared to ^{177}Lu-PSMA-617, C20 was associated with a significantly lower PSA response rate but the difference in objective response was not statistically significant (**Figure 3**).
- In sensitivity analyses removing the PR.21 trial,[7] differences in both PSA and objective response were non-significant, with RRs of 0.71 (95% CI: 0.35, 1.43) and 0.86 (95% CI: 0.35, 2.11), respectively.
- There was no statistically significant difference in PSA response between C20 and radium-223 + docetaxel (**Figure 3**).
- The PFS differences between ^{177}Lu-PSMA-617 and C20 were not statistically significant (**Figure 4**).
- An OS signal was observed but given the sparse four-study network and cross-trial heterogeneity, it should be interpreted as exploratory and hypothesis-generating rather than evidence of superiority (**Figure 4**).

Figure 4: ITC Results for OS and PFS

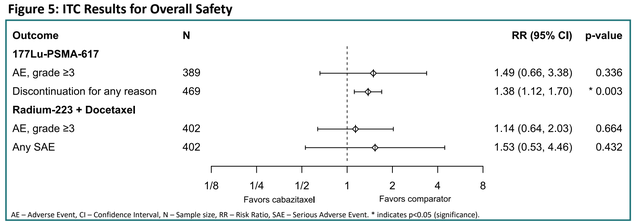


CI – Confidence Interval, HR – Hazard Ratio, N – Sample size, OS – Overall Survival, PFS – Progression-Free Survival. *indicates p<0.05 (significance).

ITC – Safety Findings

- C20 was associated with significantly greater risk of treatment discontinuation due to any reason vs. ^{177}Lu-PSMA-617 (**Figure 5**).
- Although the point estimate numerically favored ^{177}Lu-PSMA-617, no significant difference in grade ≥3 AEs was observed between C20 and ^{177}Lu-PSMA-617 (**Figure 5**).
- Compared to radium-223 + docetaxel, there was no statistically significant difference with respect to the risk of grade ≥3 AEs or SAEs (**Figure 5**).
- ITCs of specific safety events did not reach statistical significance except for all-grade alopecia and dyspnea (significantly higher risk for C20 and radium-223 + docetaxel, respectively) (data not shown).

Figure 5: ITC Results for Overall Safety



AE – Adverse Event, CI – Confidence Interval, N – Sample size, RR – Risk Ratio, SAE – Serious Adverse Event. * indicates p<0.05 (significance).

Discussion & Directions

- The OS/PFS divergence for C20 vs. ^{177}Lu-PSMA-617 may reflect differences in patient populations, endpoint definitions, or subsequent therapies rather than a true treatment effect; and combined with the sparse four-trial network supports an exploratory, hypothesis-generating interpretation of the OS signal rather than a claim of superiority.
- The dissociation between PSA response and survival reinforces the need to evaluate multiple efficacy endpoints rather than PSA alone when assessing clinical benefit.
- No statistically significant differences in major safety outcomes were identified between C20 and comparator therapies.
- Treatment selection should remain guided by patient characteristics, comorbidities, and goals of care rather than assumed tolerability differences.

Strengths

- To our knowledge, this is the first SLR and ITC to evaluate NCCN-endorsed systemic therapies in docetaxel-naïve, biomarker-unselected mCRPC after progression on prior ADT and/or ARPI.
- The analysis provides comparative evidence in a setting where direct head-to-head data remain limited.

Limitations

- The available evidence network was limited to four connected trials and included both PSMA-selected and biomarker-unselected populations, potentially affecting transitivity assumptions.
- Between-trial differences in patient characteristics, treatment era, concomitant prednisone use, outcome definitions, treatment duration and subsequent therapies may have introduced uncertainty into comparative estimates.

Future Directions

- Future RCTs incorporating taxane-based standards of care as comparator arms are needed to better define the optimal sequencing of taxanes, radioligand therapy, and other NCCN-endorsed treatments in docetaxel-naïve mCRPC.
- Additional research evaluating patient-reported outcomes and quality of life would further inform treatment decision-making.

Conclusions

- Cabazitaxel 20 mg/m^2 demonstrated lower PSA response vs. ^{177}Lu-PSMA-617, but not in sensitivity analyses, with no significant PFS differences. No significant efficacy differences were observed vs. radium-223 plus docetaxel. Findings from FIRSTANA support a favorable tolerability profile for cabazitaxel 20 mg/m^2 relative to higher-dose taxanes.
- The nominal OS signal favoring cabazitaxel 20 mg/m^2 vs. ^{177}Lu-PSMA-617 remains exploratory given the sparse network and cross-trial heterogeneity and cannot establish superiority.
- These findings reinforce the need for individualized treatment selection and highlight the need for head-to-head comparisons to better define the relative roles of cabazitaxel, ^{177}Lu-PSMA-617, radium-223-based strategies, and other guideline-endorsed options in this population.

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Disclosures

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