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Comparison of Survival Outcomes for [^{177}Lu]Lu-PSMA-617 vs. Other Systemic Treatments in Post-Taxane Metastatic Castration-Resistant Prostate Cancer Setting: A Bayesian Network Meta-Analysis

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KEY FINDINGS & CONCLUSIONS

- ^{177}Lu-PSMA-617 is associated with statistically significant OS and rPFS gain vs CABA, MIT and ARPi
  - Scenario analysis results are consistent with main analysis results and indicate efficacy benefit in favor of ^{177}Lu-PSMA-617
  - ^{177}Lu-PSMA-617 can be considered as a promising treatment option among patients with PSMA positive mCRPC previously treated with at least one ARPi and one or two taxane regimens

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INTRODUCTION

- Prostate cancer (PC) is the second most frequently diagnosed cancer in men, leading to approximately 397,000 annual deaths worldwide.[1]
- The treatment of PC is dependent upon disease location, stage, grade, prostate-specific antigen (PSA) level, and other patient-related considerations.[2,3] Patients with mCRPC that progress after androgen deprivation therapy (ADT), androgen receptor pathway inhibition (ARPi), and taxane treatments have very limited treatment options.[4]
- Numerous treatment options are available for second-line mCRPC, yet optimal sequencing remains an unmet medical need.
- The VISION trial[5], a randomized, phase III, open label study, demonstrated significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) with [^{177}Lu] Lu-PSMA-617 (^{177}Lu-PSMA-617) plus standard of care(SoC) vs. SoC alone among patients with prostate-specific membrane antigen (PSMA) positive mCRPC previously treated with at least one ARPI and one or two taxane regimens.
- A Bayesian network meta-analysis (BNMA) was conducted to determine the relative efficacy of ^{177}Lu-PSMA-617 vs. other available mCRPC treatment options.

METHODS

1. Systematic Literature Review (SLR)

- An SLR of English language articles was conducted in the MEDLINE® (including MEDLINE® In-Process and other non-indexed citations), EMBASE, and Cochrane Central Trials Register electronic databases (from database inception to 5th April 2021).
- Only phase III randomized controlled trials (RCTs) assessing pharmacological treatments in patients with mCRPC were included. Two independent reviewers performed the screening with any discrepancies reconciled by a third independent reviewer. Data from the included studies were extracted into a pre-defined extraction grid.
- Study selection criteria based on the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) were used to guide study selection and search strategies to identify potentially relevant publications (**Table 1**).
- The choice of comparators were based upon the inputs received from a Health Technology Assessment (HTA) agency and were limited to ARPi's, cabazitaxel (CABA) and mitoxantrone (MIT).

2. Feasibility Assessment

A transparent, stepwise, and reproducible methodology was utilized for feasibility assessment. Overall, this was conducted in two key steps:

1. To assess the possibility of constructing a network of interlinked RCTs. Including VISION, overall, six RCTs were identified in the SLR and were evaluated for inclusion into the NMA feasibility. The master network diagram (n= 6 RCTs) is provided in **Figure 2**. To include the VISION trial in the NMA, only the patients receiving ARPi as part of SoC were considered for a connected network.
2. Comparison of study and patient characteristics were carried out to assess for differences in study characteristics and imbalances in the distribution of treatment effect modifiers. Other intermediate steps that were considered included:
   - Clinical heterogeneity: Various baseline parameters were evaluated to assess the clinical heterogeneity between the studies included in the NMA. These parameters included median age, median Gleason score, mean prostate specific antigen (PSA) values, prior treatment status, and ECOG performance status scores.
   - Similarity of outcomes assessment across trials.
   - Heterogeneity assessment between reference arms.
   - Proportional hazards (PH) assumption testing.

3. Network Meta-Analysis (Bayesian)

To assess the relative efficacy vs. comparators, BNMA was used to compare multiple treatments simultaneously. BNMA can synthesize all available evidence in a single coherent analysis, potentially offering a more comprehensive view of the relative efficacy of various interventions.

- Efficacy outcomes analyzed were OS and rPFS. As both efficacy outcomes were time-to-event (or survival) endpoints, log cumulative hazard plots and Schoenfeld residual plots for each RCT were tested for PH assumption for OS and rPFS.
- BNMA assuming constant hazard ratios (HRs) over time was conducted with fixed effects model (FEM) and random effects model (REM).
- The results of the BNMA were based on 100,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence was assessed by visual inspection of trace plots.
- Results based on FEM were preferred over REM due to limited data points and were used to compare OS and rPFS for ^{177}Lu-PSMA-617 vs. comparators. League tables for outcomes expressed in HR with 95% credible interval (CrI) were developed to assess relative efficacy between comparators.
- Scenario analyses were additionally conducted to determine the robustness of the results.

Table 1. PICOS inclusion criteria

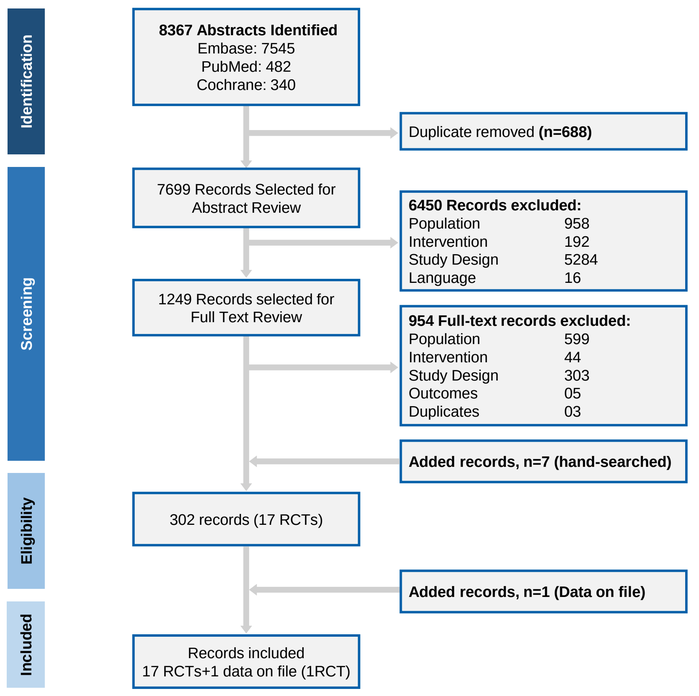
Parameter	Inclusion Criteria for SLR		Eligibility Criteria for NMA
Population	Adult males (≥18 years old) with pre-treated, progressive mCRPC		
Intervention and Comparator	No restrictions in terms of intervention or comparator		^{177}Lu-PSMA-617 compared with the following comparators: • CABA • MIT • ARPi
Outcomes	**Efficacy** • Objective response rate • OS • rPFS • Resistant disease • Time to (PSA) progression • Time to tumor progression • Time to symptomatic keletal events • PSA response • Disease control rate • Patients with symptomatic skeletal events	• Patients with tumor or PSA progression • Time to first response • Time to remission • Progressive disease • Time to treatment failure • Stable disease • Time to pain progression **Safety/tolerability** • Adverse events (Grade 3+, all grades) • Discontinuations due to AEs	The following outcomes were of interest for the NMA: • OS • rPFS
Study Design	RCTs (Phase III)		
Language	English		

RESULTS

1. Evidence based on the SLR

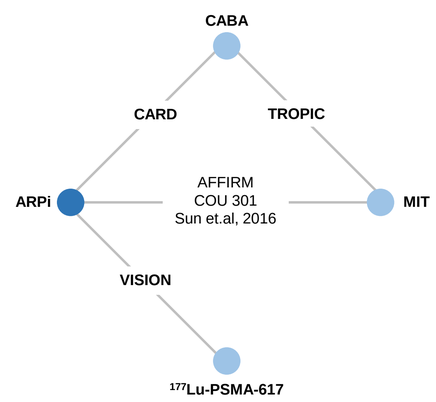
- A total of 302 articles were identified and included in the SLR, representing 17 unique phase III RCTs (**Figure 1**).
- For the current NMA, only trials evaluating intervention and comparators of interest (specifically, ^{177}Lu-PSMA-617, CABA, MIT, and ARPi) were included. Thus, the evidence base for the NMA comprised of six trials **(Figure 2)**. All six trials reported OS, whilst five studies reported rPFS, with Kaplan-Meier curves reported for PH assumption and HRs (required for constant HR NMA).

Figure 1: PRISMA flow



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized controlled trial

Figure 2: Overall network of connected studies informing evidence



*Abbreviations: ARPi: Androgen receptor pathway inhibitors: CABA: Cabazitaxel; MIT: Mitoxantrone; *SoC is referred as ARPi*

2. Feasibility Assessment

- The key takeaway from the feasibility assessment was the difference in the distribution of baseline mean PSA levels and median Gleason score (<=7) among six trials. Assessment of clinical heterogeneity further showed that Sun *et al.* 2016 had missing baseline mean PSA level, as well as a significantly lower proportion of patients with median Gleason score (<=7).
- Due to a limited number of studies (n<10), a meta-regression accounting for the differences in baseline characteristics such as mean PSA (ng/ml) and Gleason score could not be performed.
- For both the OS and rPFS networks, the PH assumption was valid for most of the studies except COU-301 (OS) and all six studies were connected via a common treatment node ARPi.
- Scenario analysis for OS and rPFS based on excluding the COU-301 study with non-proportional hazards and Sun *et.al*, 2016 was conducted.

3. Network Meta-Analysis

Overall survival and radiographic progression-free survival

- Analysis of constant HR for OS based on BNMA using FEM showed that the comparison of ^{177}Lu-PSMA-617 versus all three comparators significantly favored ^{177}Lu-PSMA-617 vs. MIT (0.39, 95% CrI: [0.29–0.51]), ARPi (0.54, 95% CrI: [0.41–0.70]), and CABA (0.59, 95% CrI: [0.43–0.80]) (**Table 2**).
- The results from the analysis for rPFS were similar and indicated that ^{177}Lu-PSMA-617 was associated with statistically significantly improved rPFS vs. MIT (0.30, 95% CrI: [0.21–0.43]), ARPi (0.53, 95% CrI: [0.37–0.75]), and CABA (0.48, 95% CrI: [0.33–0.71]) (**Table 2**).
- Scenario analysis results for OS based on exclusion of Sun *et al.,* 2016 and COU-301, both comparing MIT vs. ARPi and scenario analysis results for rPFS based on exclusion of COU-301 were consistent with the main analysis results (**Table 3**).

Table 2. Base case Bayesian NMA results

Endpoint	^{177}Lu-PSMA-617 vs		
	CABA	ARPi	MIT
OS HR (95% CrI):	0.59 (0.43, 0.80)	0.54 (0.41, 0.70)	0.39 (0.29, 0.51)
rPFS HR (95% CrI):	0.48 (0.33, 0.71)	0.53 (0.37, 0.75)	0.30 (0.21, 0.43)

Table 3. Scenario Analysis Bayesian NMA results

Endpoint	^{177}Lu-PSMA-617 vs		
	CABA	ARPi	MIT
OS HR (95% CrI):	0.58 (0.41, 0.80)	0.54 (0.41, 0.71)	0.38 (0.28, 0.52)
rPFS HR (95% CrI):	0.43 (0.29, 0.64)	0.53 (0.37, 0.76)	0.26 (0.18, 0.38)

Discussion and Limitations

The results from the NMA demonstrated statistically significant rPFS and OS benefit in favor of ^{177}Lu-PSMA-617 vs. other comparators among patients with PSMA positive mCRPC previously treated with at least one ARPi and one or two taxane regimens. Whilst direct comparative evidence to inform treatment decisions in post-taxane mCRPC setting is lacking, these findings suggest that ^{177}Lu-PSMA-617 may yield improved survival outcomes for these patients.

- Due to the differences in the distribution of effect modifiers and prognostic variables across the included studies, the results of the NMA should be interpreted with caution.
- A network meta-regression adjusting for these differences was not feasible due to the small number (n<10) of studies included in the NMA.
- The TheraP trial, a multicenter, randomized phase 2 trial in Australia comparing ^{177}Lu-PSMA-617 vs. cabazitaxel, was not included since it did not meet the eligibility criteria for the SLR.[6]

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Disclosures

Valéry Risson, Aran OLoughlin, Ankur Khare, and Parth Joshi are employees of Novartis. Vikalp Maheshwari and Abhiroop Chakravarty are employees of PAREXEL.

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