CO135

A Systematic Literature Review (SLR) and Network Meta-Analysis (NMA) in First-Line (1L) Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Objective

To estimate the comparative efficacy and safety of TALA+ENZA in 1L mCRPC by conducting an SLR and NMA.

Conclusions

Results suggest that TALA+ENZA has a superior efficacy profile but higher rates of hematological toxicities compared to other 1L treatments approved or expected to be approved across multiple endpoints analyzed, indicating its therapeutic potential for the treatment of patients in 1L mCRPC.

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Background

- Approximately 20% of new cancer cases in Europe are prostate cancers.[1]
- Patients with prostate cancer can progress to the advanced mCRPC form which is associated with poor prognosis and poor quality of life.[2]
- Despite the availability of treatment options, mCRPC diagnoses continue to have a high mortality rate, indicating a need for better treatment options.[2]
- Poly (ADP-ribose) polymerase inhibitors (PARPi) are an emerging class of novel therapies in the mCRPC treatment landscape.
- The FDA approved PARP inhibitor - talazoparib, has demonstrated benefit in combination with enzalutamide (TALA+ENZA) for the 1L treatment of patients with mCRPC (TALAPRO-2; NCT03395197).[3]
- Head-to-head trials evaluating the comparative efficacy and safety of all established mCRPC treatments with TALA+ENZA are crucial for informing clinical decision-making.
- However, since TALA+ENZA has only been directly compared with ENZA, NMAs are leveraged to fill this evidence gap.[4]

Materials and Methods

SLR

- Embase, MEDLINE®, and Cochrane CENTRAL were searched from inception to October 2022 using Ovid® and supplemented with hand-searching of grey literature sources.
- Articles were selected based on pre-specified PICOS criteria (**Table 1**) and reviews aligned with the PRISMA statement[5-6] as well as the Cochrane guidelines[7] (PROSPERO registration: CRD42021283512).

Table 1: PICOS Criteria

Population	Adult (≥18) male mCRPC patients who are treatment naïve in the mCRPC setting
Interventions/ Comparators	Any treatments available or under investigation for mCRPC
Outcomes	Endpoints pertaining to survival (OS, PFS, rPFS, PFS2), clinical response (ORR, DoR, PSA response, proportion of patients with PSA response ≥50%), other clinical outcomes (TPP, TCC, time to initiation of antineoplastic therapy, time to first SSE, opioid use for cancer pain), safety (incidence of AEs, SAE, AEs leading to discontinuation), and PROs (HRQoL [eg, EQ-5D, FACT-P, SF-36, EORTC QLQ-C30, EORTC QLQ-PR25, BPI-SF, PGI-S, etc.])
Study Design	RCTs (Phase II, II/III, III) and conference abstracts of RCTs

FEASIBILITY ASSESSMENT

- Studies identified from the SLR were qualitatively assessed for between-trial heterogeneity to ensure the evidence meets the exchangeability assumption.[8]
- Assessment across the following factors were validated by clinical expert opinion: trial design characteristics, patient eligibility criteria, baseline patient characteristics, baseline risk (if appropriate), and outcome characteristics, and connection to the main network with TALA+ENZA.

NMA

- Studies deemed sufficiently similar or feasible were then considered for Bayesian random- and fixed-effects or frequentist fixed-effects NMAs.[9]
- Outcomes assessed included radiographic progression-free survival (rPFS), overall survival (OS), and grade ≥3 adverse events (AE) such as anemia, asthenia, decreased appetite, fatigue, nausea.
- Hazard ratios (HRs) for rPFS and OS, discrete HRs for grade ≥3 AEs, 95% credible or confidence intervals (CrI or CI), and Surface Under the Cumulative Ranking Curve (SUCRA) were calculated. The most recent data cutoff (DCO) for TALAPRO-2 (DCO: 16/08/22 for rPFS and AEs; DCO: 28/03/23 for OS) and comparators informed the analyses.

Abbreviations: 1L = first-line; AA+DEX = Abiraterone acetate 1000 mg plus Dexamethasone 0.5 mg once daily; AAP = abiraterone acetate plus prednisone; AAP2.5BID = Abiraterone acetate 1000 mg plus Prednisone 2.5 mg twice daily; AAP5QD = Abiraterone acetate 1000 mg plus Prednisone 5 mg once daily; AAPnoLHRH = Abiraterone acetate 1000 mg oral daily + Prednisone 5 mg oral twice daily with no LHRH therapy; AAPorENZA = abiraterone acetate plus prednisone or enzalutamide; AE = adverse event; APA+AAP = Apalutamide 240mg oral daily + Abiraterone acetate 1000mg oral daily + Prednisone 5mg oral twice daily; BSC = best supportive care; BIC = Bicalutamide 50 mg; BPI-SF = Brief Pain Inventory (Short Form); CABA20 = Cabazitaxel 20 mg/m^2; CABA25+AAP = Cabazitaxel 25mg/m2 intravenous every three weeks + Abiraterone Acetate 1000mg oral daily + Prednisone 5mg oral twice daily; CI = confidence interval; CrI = credible interval; DCO = data cutoff; DOC30+PS = Docetaxel 30 mg/m^2 plus prednisone; DOC50+PL10 = Docetaxel 50mg/m^2 intravenous once every two weeks + Prednisolone 10mg oral daily; DOC75+PS = Docetaxel 75 mg/m^2 plus prednisone; DoR = duration of response; ENZA = Enzalutamide 160 mg; ENZA+AAP = Enzalutamide 160 mg and Abiraterone acetate 1000 mg plus Prednisone; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30-question; EORTC QLQ-PR25 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate-specific 25-question; EQ-5D = EuroQoL 5-dimension; ESMO = European Society for Medical Oncology; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FDA = Food and Drug Administration; HR = hazard ratio; HRQoL = health-related quality of life; IPA+AAP = Ipatasertib 400mg oral daily + Abiraterone acetate 1000mg oral daily + Prednisone/Prednisolone 5mg oral twice daily; mCRPC = metastatic castration-resistant prostate cancer; MIT12+PS = Mitoxantrone 12mg/m^2 intravenous once every three weeks + Prednisone/Prednisolone 5mg oral twice daily/10mg oral daily; MIT14+HC = Mitoxantrone 14mg/m^2 intravenous once every three weeks + Hydrocortisone 40mg oral daily; NMA = network meta-analysis; OLAP+AAP = Olaparib 300mg oral twice daily + Abiraterone acetate 1000mg oral daily + Prednisone/Prednisolone 5 mg oral twice daily; OR = odds ratio; ORR = objective response rate; OS = overall survival; PARPi = poly-ADP ribose polymerase inhibitors; PFS = progression-free survival; PFS2 = progression-free survival on next line of therapy; PGI-S = Patient Global Impression of Severity; PICOS = population, intervention, comparator, outcome, study design; PRISMA = Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses; PRO = patient-reported outcome; PSA = prostate-specific antigen; Ra55+AAP = Radium-223 55 kBq/kg every four weeks + Abiraterone acetate 1000mg oral daily + Prednisone/Prednisolone 5mg oral twice daily; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; SAE = serious adverse event; SF-36 = 36-Item Short-Form Health Survey; SIP-T = Sipuleucel-T; SLR = systematic literature review; SSE = symptomatic skeletal event; SUCRA = surface under the cumulative ranking curve; TALA+ENZA = Talazoparib 0.5mg daily + Enzalutamide 160mg oral daily; TCC = time to initiation of cytotoxic chemotherapy; TPP = time to PSA progression; vs = versus.

Results

SLR AND FEASIBILITY ASSESSMENT

- Thirty-eight randomized controlled trials (RCTs) with published results at the time of the SLR plus data for TALAPRO-2 provided by Pfizer were considered for NMAs.
- Six trials were excluded during feasibility assessment due to eligibility criteria, or disconnection from the main TALA+ENZA network across all outcomes; therefore, 33 RCTs informed the NMAs.

NMA

rPFS

- The rPFS network included 13 RCTs and 14 treatments (**Figure 1A**).
- TALA+ENZA was associated with numerical improvements in rPFS vs all comparators, statistically significant improvements vs six treatments, and the highest likelihood of being the top ranked therapy (**Figure 2A**).

OS

- The OS network included 20 RCTs and 18 treatments (**Figure 1B**).
- TALA+ENZA was associated with numerical improvements in OS vs all except one comparator (DOC50+PL10), statistically significant improvements vs two treatments, and the second highest likelihood of being the top ranked therapy (**Figure 2B**).

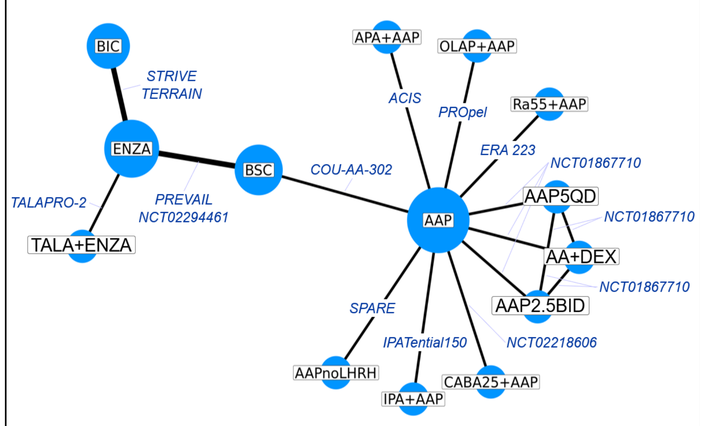
–*Note: DOC50+PL10 is a non-standard docetaxel regimen investigated in the PROSTY trial.*

AE (Grade ≥3)

- TALA+ENZA was associated with higher rates of anemia and asthenia vs all comparators within each respective outcome network.
- Across multiple comparators, TALA+ENZA was associated with higher rates of fatigue.
- For decreased appetite and nausea, TALA+ENZA was associated with lower rates of the AE vs all but one comparator (ENZA and BSC, respectively).
- Only 6 out of 10 comparisons in each network for anemia and asthenia were statistically significant.
- For fatigue, decreased appetite, and nausea, none of the comparisons were statistically significant.

Figure 1. Network Diagrams for rPFS and OS

A. rPFS



B. OS

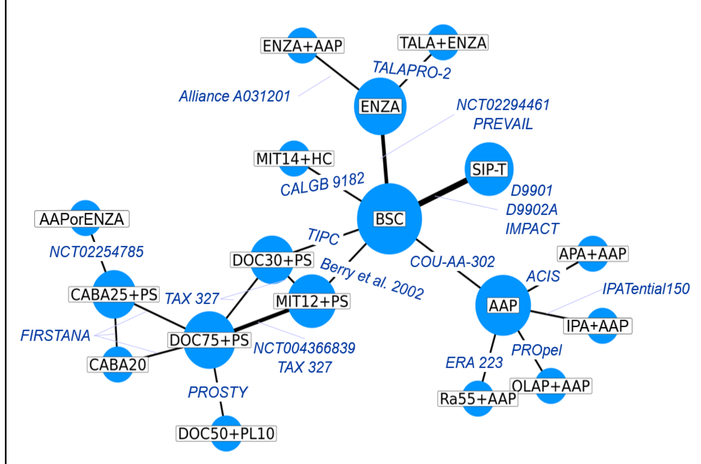
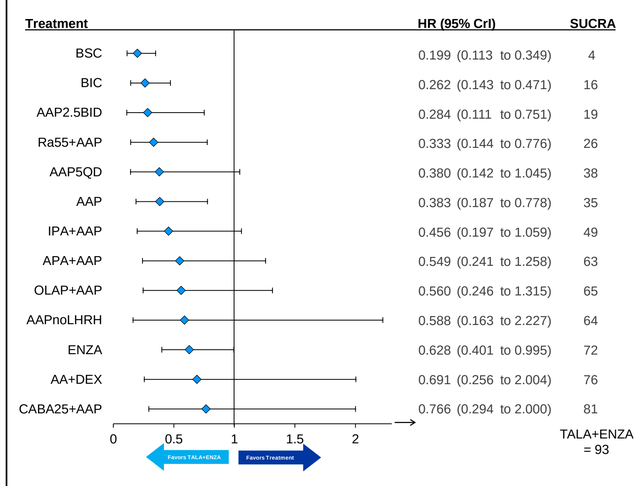
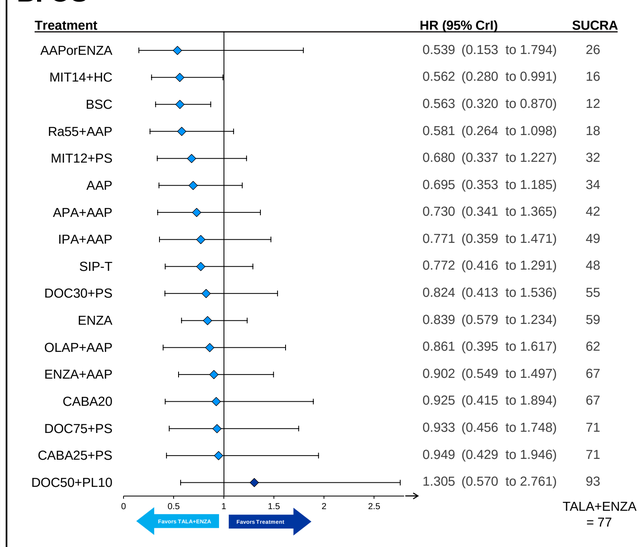


Figure 2. Random Effects Forest Plot and SUCRA for TALA+ENZA vs. Other Treatments

A. rPFS



B. OS



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Disclosures: EC has participated in advisory boards for AstraZeneca, Bayer, Daiichi-Sankyo, Janssen, MSD, Pfizer & Telix, received research funding from Bayer, Janssen, Synlab, & Pfizer, received speaker fees from AstraZeneca, Astellas, Bayer, Clovis, Janssen, Novartis, Pfizer & Telix, and received travel, accommodation, and expenses from AstraZeneca & Janssen. IAS, JE, SP, and SC are employees of EVERSANA, Canada, which was contracted by Pfizer to work on this project. JN is supported by the 2021-2023 University of Illinois Chicago-Pfizer Fellowship. AN is an employees of Pfizer and owns Pfizer stock.

Acknowledgments: This study was sponsored by Pfizer Inc. For TALAPRO-2, enzalutamide was provided by Astellas Pharma Inc. Assistance with the literature review and feasibility assessment was provided by Teresa Kangappaden, Krista Tantakoun, Karen Chiang, Christopher Olsen, Amrita Debnath, and Joanna Bielecki.

Presented at ISPOR EU 2023 • November 12–15, 2023 • Copenhagen, Denmark