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Predicting Treatment Effects from Surrogate Endpoints in First-Line (1L) Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Imtiaz A. Samjoo,[1] Tim Disher,[1] Elena Castro,[2] Jenna Ellis,[1] Stefanie Paganelli,[1] Jonathan Nazari,[3] Alexander Niyazov.[3]

[1]EVERSANA™, Burlington, Ontario, Canada; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Pfizer, Inc., New York, New York, USA.

Objective

(1) To predict the unreported effect estimates of rPFS and OS using advanced surrogate modelling techniques; and (2) to report results of an SLR and NMA utilizing these estimates to quantify the comparative efficacy of talazoparib in combination with enzalutamide (TALA+ENZA) in 1L mCRPC treatment.

Conclusions

Using advanced surrogate modelling techniques to impute missing rPFS and OS data in historical trials allows a comprehensive evidence base for use in comparative analyses and cost-effectiveness models to help aid decision-making.

Non-author presenter: Chris Cameron

Email: chris.cameron@eversana.com

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Background

- Despite the emergence of novel treatment options such as poly (ADP-ribose) polymerase inhibitors (PARPi), older therapies approved within the last 15 years continue to be relevant for 1L mCRPC treatment in various markets.[1]
- Choice of intervention varies considerably for patients, leading to additional challenges related to treatment recommendations and reimbursement.
- To ensure decisions for selecting therapies are well informed, health technology assessments require a comprehensive evidence base inclusive of analyses and models quantifying relative treatment effectiveness.
- However, data from historical trials may be missing modern endpoints such as radiographic progression-free survival (rPFS), precluding comparative analyses of treatment effects via network meta-analyses (NMA).
- In such cases, multivariate meta-analysis methods could be utilized to impute unavailable rPFS data by leveraging evidence from correlated outcomes such as overall survival (OS).[2]
- Imputed data could then provide a comprehensive synthesis of relevant evidence, allowing the incorporation of additional treatments in NMAs, the results of which could inform health economic decision models.

Materials and Methods

SYSTEMATIC LITERATURE REVIEW & FEASIBILITY ASSESSMENT

- MEDLINE®, Embase, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews (inception to October 2022) were searched using Ovid® and supplemented with handsearching of grey literature sources.
- Study selection were based on pre-specified PICOS criteria (**Table 1**), and reviews followed the PRISMA statement[3-4] and Cochrane guidelines[5] (PROSPERO registration: CRD42021283512).
- Qualitative assessments for between-trial heterogeneity were conducted to verify the evidence meets the exchangeability assumption.[6]

SURROGATE MODEL

- Using the Daniels and Hughes Surrogate Model,[7] treatment effects on rPFS and OS in studies missing these outcome results were predicted through a model fitted to data from trials reporting both endpoints.
- Predictions follow three main assumptions, namely, that the target outcomes, rPFS and OS, are missing at random in historical trials, are correlated, and follow a common bivariate distribution.

Abbreviations: 1L = first-line; AA = Abiraterone acetate 1000 mg; 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; AAP5BID = Abiraterone acetate 1000 mg plus Prednisone 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; DOC30+PS = Docetaxel 30 mg/m2 plus prednisone; DOC50+PL10 = Docetaxel 50mg/m2 intravenous once every two weeks + Prednisolone 10mg oral daily; DOC75+PS = Docetaxel 75 mg/m2 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; 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/m2 intravenous once every three weeks + Prednisone/Prednisolone 5mg oral twice daily/10mg oral daily; MIT14+HC = Mitoxantrone 14mg/m2 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; ORR = objective response rate; OS = overall survival; 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.

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- Missing data are imputed in a stepwise manner:
  - First, rPFS is predicted based on the modeled treatment effect on OS.
  - Second, OS is predicted based on the imputed rPFS results.
  - Lastly, imputed plus reported data are used to conduct NMAs (see Poster CO135)

Table 1: PICOS Criteria

Population	Adult (≥18) male patients with mCRPC 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

Results

LITERATURE SEARCH AND FEASIBILITY ASSESSMENT

- Thirty-eight RCTs with published data at the time of the SLR plus data for TALAPRO-2 (TALA+ENZA) met the eligibility criteria.
- Fourteen studies were excluded during the feasibility assessment due to eligibility criteria, unavailability of outcome results, method of outcome reporting, or disconnection from the main TALA+ENZA network.
- Of the 25 remaining eligible trials, eight RCTs reported both rPFS and OS, five RCTs reported rPFS only and 12 RCTs reported OS only.

SURROGATE MODEL

PREDICTION OF TREATMENT EFFECT

rPFS

- rPFS was predicted for 10 comparators from the 12 RCTs that reported OS only (**Table 2**).

OS

- OS was predicted for six comparators from the 5 RCTs that reported rPFS only (**Table 2**).

Table 2. List of Included Studies Missing rPFS or OS Values

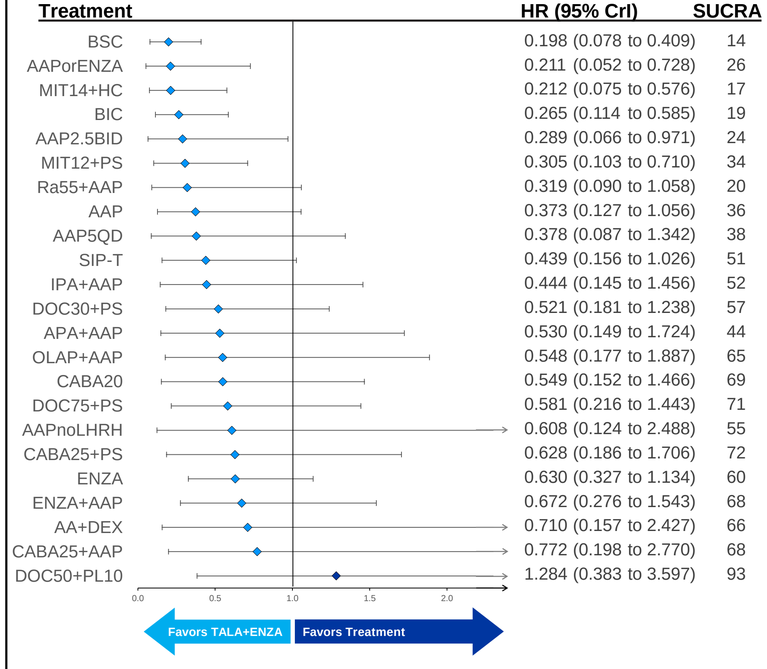
Trial	Missing Outcome	Treatment	Daniel & Hughes Model Estimates	
NCT01867710	OS	AAP2.5BID vs AAP5QD	1.339 (0.942-1.902)	*P = 0.103*
		AA+DEX vs AAP5QD	0.540 (0.331-0.883)	*P = 0.014*
		AAP5BID vs AAP5QD	0.990 (0.541-1.811)	*P = 0.977*
SPARE; NCT02077634	OS	AAP vs AAPnoLHRH	0.861 (0.637-1.164)	*P = 0.336*
TERRAIN; NCT01288911	OS	ENZA vs BIC	0.751 (0.550-1.024)	*P = 0.0697*
STRIVE; NCT01664923	OS	ENZA vs BIC	0.623 (0.456-0.852)	*P = 0.0031*
NCT02218606	OS	CABA25+AAP vs AAP	0.775 (0.568-1.059)	*P = 0.110*
Alliance A031201; NCT01949337	rPFS	ENZA+AAP vs ENZA	0.947 (0.769-1.167)	*P = 0.623*
CALGB 9182	rPFS	MIT14+PS vs Hydrocortisone	0.914 (0.743-1.124)	*P = 0.402*
Berry et al. 2002	rPFS	MIT12+PS vs Prednisone	0.754 (0.610-0.932)	*P = 0.009*
TAX 327	rPFS	DOC75+PS vs MIT12+PS	0.677 (0.549-0.835)	*P < 0.001*
		DOC30+PS vs MIT12+PS	0.754 (0.613-0.927)	*P = 0.007*
NCT00436839	rPFS	DOC75 vs MIT	0.427 (0.347-0.527)	*P < 0.001*
PROSTY; NCT00255606	rPFS	DOC75+PS vs DOC50+PL10	2.168 (1.747-2.692)	*P < 0.001*
TIPC	rPFS	DOC30+PS vs BSC	0.327 (0.267-0.400)	*P < 0.001*
FIRSTANA; NCT01308567	rPFS	CABA25+PS vs DOC75+PS	0.943 (0.762-1.165)	*P = 0.597*
		CABA20 vs DOC75+PS	1.107 (0.896 to 1.367)	*P = 0.352*
NCT02254785	rPFS	CABA25+PS vs AAPorENZA	0.340 (0.274-0.420)	*P < 0.001*
D9901; NCT00005947	rPFS	SIP-T vs BSC	3.274 (2.661-4.028)	*P < 0.001*
D9902A; NCT01133704	rPFS	SIP-T vs BSC	1.756 (1.431-2.155)	*P < 0.001*
IMPACT; NCT00065442	rPFS	SIP-T vs BSC	0.563 (0.457-0.694)	*P < 0.001*

NMA

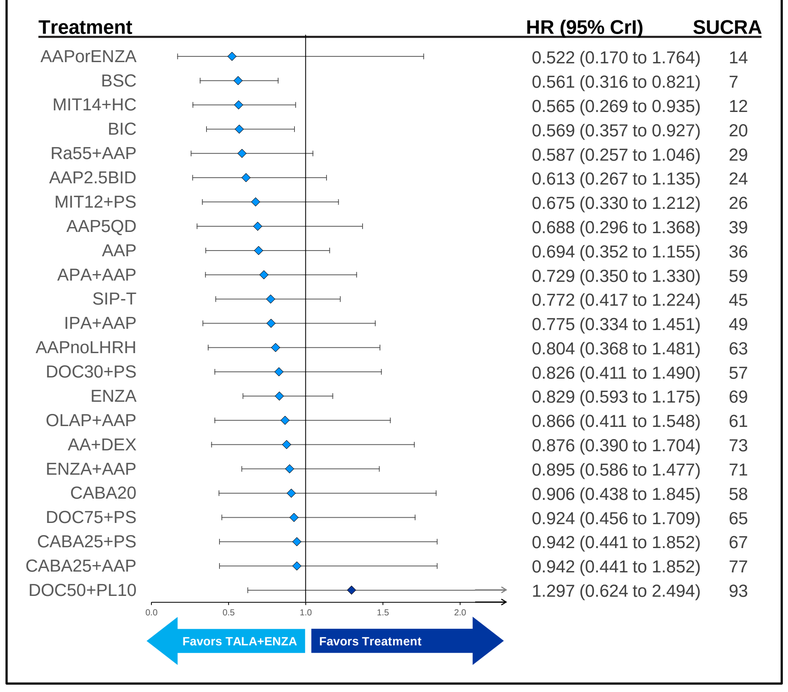
- TALA+ENZA was associated with numerical improvements in rPFS and in OS vs all except one comparator (DOC50+PL10) within each respective outcome network, and the second highest likelihood of being the top ranked therapy (**Figure 1**).
  - *Note: DOC50+PL10 is a non-standard docetaxel regimen investigated in the PROSTY trial.*
  - TALA+ENZA was associated with statistically significant improvements in rPFS vs six treatments (**Figure 1A**)
  - TALA+ENZA was associated with statistically significant improvements in OS vs three treatments (**Figure 1B**)

Figure 1: Random Effects Forest Plot and SUCRA for TALA+ENZA vs. Other Treatments

A. rPFS



B. OS



Limitations

- Although a thorough feasibility assessment was conducted and results were validated by clinical opinion, some differences in baseline characteristics were observed. The impact of the heterogeneous characteristics was not explored in this study.
- The network structure was sparse and connections between treatments were typically informed by a single trial. Furthermore, many trials did not share a central common comparator (eg, BSC) resulting in substantial distances between some treatments (ie, TALA+ENZA and DOC50+PL10). This increases the potential for biased treatment effects and introduces uncertainty in the results.
- Lastly, large confidence intervals were observed for some effect estimates.