The Impact of Different Time-Varying Network Meta-Analysis Methods to Assess Talazoparib + Enzalutamide Versus Olaparib + Abiraterone in Metastatic Castration-Resistant Prostate Cancer

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Objective

- To compare the OS and rPFS of TALA+ENZA with other treatments for mCRPC when hazards are non-proportional

Conclusions

- TALA+ENZA demonstrated greater rPFS compared with ENZA and OLA+ABI, regardless of the time-varying NMA method used
- The choice of time-varying NMA method can have a meaningful impact on survival estimates
- It was not possible to reliably estimate comparative OS using time-varying NMA due to model convergence issues
- The sparse evidence base and short follow-up poses challenges for convergence of more complex models with more or non-linear parameters (e.g. second order FP-NMA or three-knot RCS-NMA). A pNMA may be preferred in such cases and more standard methods may be required (e.g. standard NMA or unanchored population-adjustment methods)

Key: ABI, abiraterone; BSC, best supportive care; CI, confidence interval; CrI, credible interval; ENZA, enzalutamide; FP, fractional polynomial; HR, hazard ratio; HTA, heath technology assessment; mCRPC, metastatic castration-resistant prostate cancer; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OLA, olaparib; OS, overall survival; PH, proportional hazards; pNMA, parametric network meta-analysis; RCS, restricted cubic spline; RCT, randomized controlled trial; rPFS, radiographic progression-free survival; TALA, talazoparib.

References:

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Introduction

- The efficacy and safety of TALA+ENZA in patients with mCRPC were evaluated in the Phase III, double-blind TALAPRO-2[1] RCT, where TALA+ENZA demonstrated improved OS and rPFS compared with ENZA monotherapy (ENZA given with placebo)
- The NICE HTA submission for TALA+ENZA required comparative analyses between TALA+ENZA and key comparators, such as OLA+ABI, to inform the cost-effectiveness analysis
- Standard NMAs were conducted to estimate the relative OS and rPFS of TALA+ENZA against OLA+ABI. Standard NMA of time-to-event endpoints assumes that the PH assumption holds across the network
- During the NICE appraisal, uncertainty was raised regarding assumptions underpinning the indirect treatment comparison for survival outcomes. As a result, the use of time-varying (non-PH) NMAs was explored to address potential violations of the proportional hazards assumption.

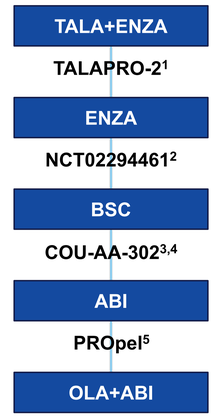
Methods

- The evidence network (Figure 1) consisted of four trials and five treatments. Only one trial supported each connection; therefore, all trials were essential to connecting TALA+ENZA with OLA+ABI
- **Three time-varying NMA methods, totaling 45 models, were fitted to the network**

Fractional polynomial NMA (FP-NMA)[6]	Restricted cubic spline NMA (RCS-NMA)[7]	Two-step parametric NMA (pNMA)[8]
First- and second-order FP-NMA models were fitted to the data. The choice of powers included all combinations from {-2, -1, -0.5, 0, 0.5, 1, 2}, giving a total of 35 models (seven and 28 for first and second order, respectively)	One-, two-, and three-knot RCS-NMA models were fitted using equally distributed knots specific to each treatment arm, based on the log of uncensored survival times	Seven "standard" parametric distributions were used for the pNMA (exponential, Weibull, gamma, Gompertz, generalized gamma, log-normal, log-logistic)

- All NMAs used Bayesian fixed-effects models due to the sparse evidence network
- For each model, survival estimates for ENZA and OLA+ABI were calculated by applying the estimated time-varying HR to the reference curve (TALA+ENZA; log-normal). Mean survival time was calculated from these curves (using the trapezium rule) and compared

Figure 1. Evidence network



Results

Model convergence and selection

- FP and RCS-NMA models did not converge for OS. Most pNMA models converged; however, estimated HRs had very wide CrIs that were not informative for decision-making, so results are not presented. Convergence issues were likely due to the lack of follow-up in NCT02294461 (median OS not reached in either arm) and sparse evidence network
- Convergence was improved for rPFS, likely because data were more mature. Less complex models (e.g. models with fewer parameters) showed enhanced convergence rates (Table 1)
- The preferred model from each method was chosen based on statistical and visual fit to the data. This included: first order p = -1 for FP-NMA, log-normal for pNMA, and two-knot for RCS-NMA

Table 1. Model convergence for rPFS

Method	Converged models[a]	Non-converged models
FP-NMA	First order p = -1, -0.5, 0	Other first order, second order
RCS-NMA	One-knot, two-knot	Three-knot
pNMA	All distributions	None

Note: [a] Assessment of model convergence was based on visual assessment of autocorrelation plots, posterior density plots, trace plots, and plots of running means.

rPFS results

- Time-varying HRs for TALA+ENZA versus both comparators were < 1 when all trials had observed data across all methods. This trend continued for most of the extrapolated period (up to 360 months) in the FP-NMA and pNMA. However, the time-varying HR 95% CrIs were wide and overlapped 1

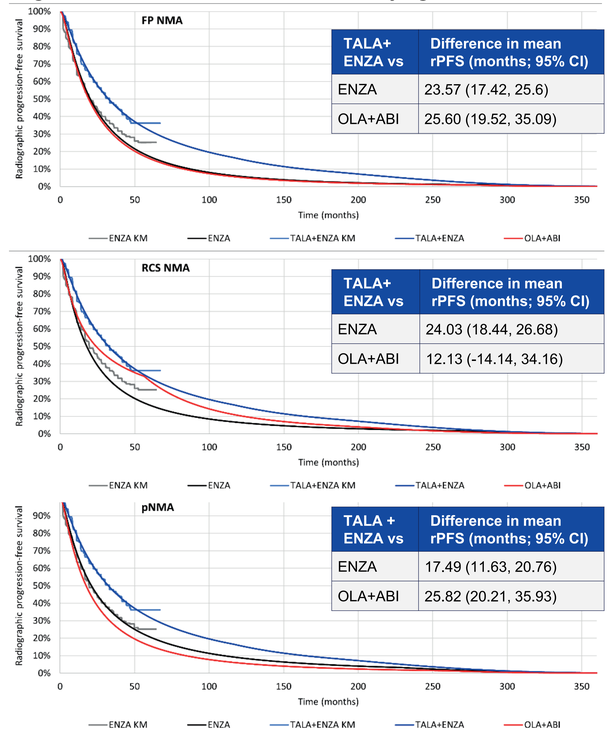
rPFS results (cont.)

- Predicted survival curves for ENZA and OLA+ABI differed across time-varying NMA models (Figure 2)
- All NMA models showed that TALA+ENZA provides longer average rPFS versus ENZA, with 95% CIs excluding 0. For TALA+ENZA vs OLA+ABI, only the RCS-NMA 95% CI included 0

Limitations

- Short follow-up in NCT02294461 and a sparse evidence network caused convergence issues, particularly for OS and models with more parameters. In the cost-effectiveness analysis, OS for comparators not in TALAPRO-2 was therefore based on time-constant HRs, estimated using either standard NMA or matching-adjusted indirect comparison
- Time-varying HRs, a key result of time-varying NMAs, and their statistical significance, can be difficult to interpret due to their multi-dimensional nature. The differences in mean survival time have been presented instead, to provide a single estimate of relative efficacy
- Deviance information criterion values across methods cannot be compared because data and likelihoods differ, posing a challenge for choosing the most suitable method[9]
- No formal HTA guidance exists for time-varying NMA methods

Figure 2. Estimated rPFS across time-varying NMA models[a]



Notes: [a] rPFS estimates were capped by OS.