Radiographic progression free survival as a surrogate endpoint for overall survival among men with Metastatic Castration-Resistant Prostate Cancer

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Background

Development of innovative therapies with long-term patient benefits (which are typically submitted for regulatory approvals with immature short-term follow up data) necessitates identification of surrogate endpoints. Determining patient benefit in the absence of death or other complications is vital in drug development and patient care. Radiographic progression-free survival (rPFS) is used as a co-primary endpoint among men with metastatic castration-resistant prostate cancer (mCRPC) in randomized clinical trials (RCT). Overall survival (OS) is accepted as the gold standard clinical endpoint, but it requires long follow-up. Results of the current analysis will provide evidence on the relationship between rPFS and OS which can be used to extrapolate long-term OS for mCRPC subjects, especially in case OS is not mature at the time of health technology assessment (HTA) submission.

Methods

A systematic literature review was carried out to find all the studies where rPFS and OS were evaluated in patients with mCRPC. Trial-level correlation analysis based on hazard ratio was carried out to evaluate if rPFS can be a surrogate endpoint for OS. This was preceded by the examination of the proportional hazards (P-H) assumption using the Schoenfeld test[1].

To choose the correlation method, normality assumption was tested by the Shapiro-Wilks test and normal Q-Q plot. Spearman correlation analysis was performed due to non-conformity to the normality assumption by OS of the included studies.

The surrogate threshold effect (STE) for the current analysis is the minimum treatment effect that is necessary on rPFS to be able to predict an OS benefit. Graphically, this is where the upper 95% CI of regression prediction line[2] for an individual trial crosses the horizontal axis representing OS benefit[3]. Weighted least squares regression equation modelled OS as a function of rPFS. The upper 95% prediction band was used to determine the minimum rPFS and OS HR, the STE, below which there would be no predicted OS benefit

In addition to the standard surrogate threshold effect (STE) framework, association was obtained by regression analysis, i.e., Daniels and Hughes (D&H) fixed effects meta-analysis[4], and bivariate random effects meta-analysis (BRMA)[5]. BRMA approach facilitated random effects while D&H method assumed fixed effects (independent prior distributions) for the treatment effect on the surrogate endpoint. BRMA Product Normal Formulation (PNF) methods were used to demonstrate the association between rPFS and OS for cross-validation of analysis.

Table 1: Strength association between outcomes (IQWiG)[6]

Correlation type	Range
High	r ≥ 0.85
Low	r ≤ 0.7
Medium	0.7 < r < 0.85

Results

- A systematic literature review of articles published on mCRPC trials from 2012 to 2022 yielded 109 studies from 260 publications.
- Further examination of available Kaplan-Meier curves and hazard ratios for OS and PFS provided 22 RCTs with requisite information for surrogacy analysis.
- P-H assumption was followed by almost all the included studies. Normality assumption was valid for rPFS (Figure 1) but was not valid for OS (Figure 2).
- Unweighted Spearman correlation rho = 0.62 and weighted Spearman correlation rho = 0.65 were obtained for association between rPFS and OS, while standard BRMA and BRMA PNF yielded similar estimates of rho=0.69, showing medium correlation among the endpoints assessed.
- The results for STE are presented in Figure 3 by a scatterplot weighted by standard error (SE) of the HR for OS. The upper and lower dotted lines are the upper and lower 95% confidence limits, the inner central blue line is the mean regression line.
- STE = 0.72 implies that rPFS HR should be less than or equal to 0.72 to have significant OS HR in the new trial.

Table 2: Correlation analysis results

Method	rho	Correlation type
Unweighted Spearman correlation	r = 0.62	Low
Weighted Spearman correlation	r = 0.65	Low
BRMA	r = 0.69	Medium
BRMA PNF	r = 0.69	Medium

Figure 1: Q-Q plot for log (rPFS)

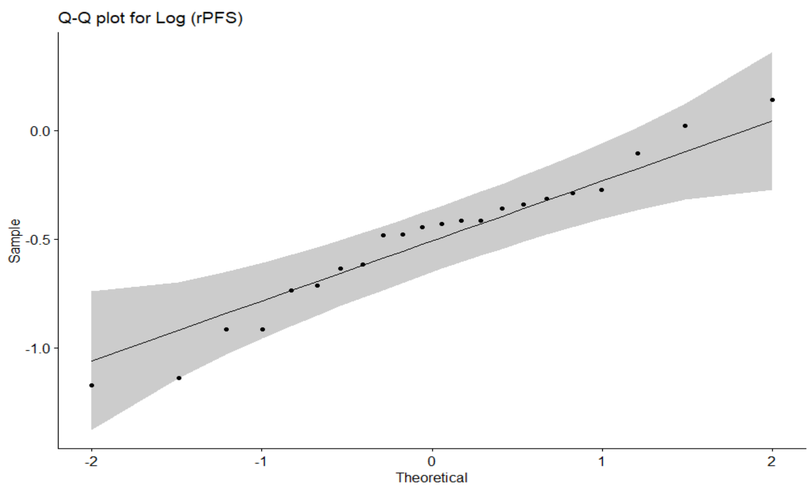


Figure 2: Q-Q plot for log (OS)

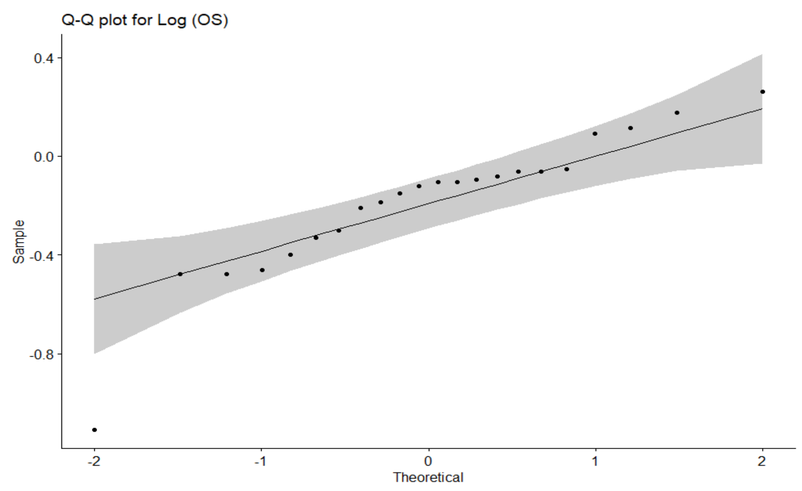
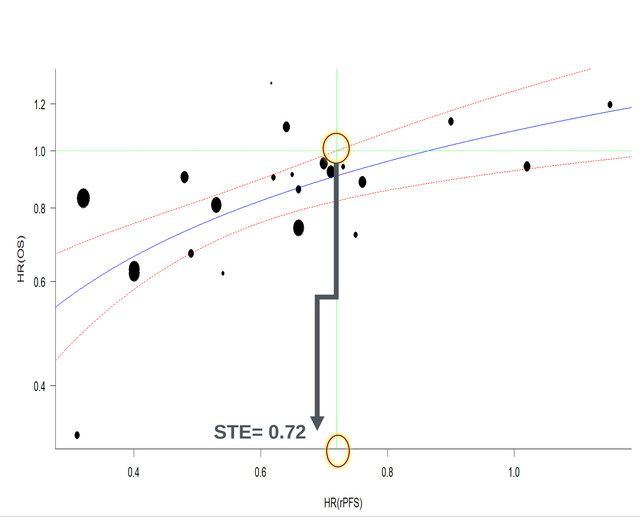


Figure 3: STE results



Conclusions

- The validation and use of surrogate endpoints for regulatory approvals to ensure timely patient access to much needed therapies in absence of complete data on primary endpoints.
- The current study demonstrates medium correlation between rPFS and OS, among mCRPC patients. Hence, in instances where OS is immature, rPFS could potentially be used as a moderate level predictor for OS.

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