Evaluating Individual-level Association Between Radiographic Progression-free Survival (PFS) and Overall Survival (OS) in Metastatic Hormone-sensitive Prostate Cancer (mHSPC): An Indirect Illness-death Modeling Approach

CO28

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Background

- mHSPC is a form of metastatic prostate cancer in which the disease is still responsive to hormone therapy. It arises when prostate cancer cells spread beyond the primary gland while retaining dependence on androgen receptor signaling.
- Since the 1990s, the cornerstone of mHSPC treatment has been androgen deprivation therapy (ADT).[1] However, treatment of mHSPC has seen significant advances in recent decades due to introduction of doublet therapy combining ADT with docetaxel, androgen receptor signaling inhibitors (ARSIs) such as abiraterone, enzalutamide, and apalutamide, and triplet therapy combining ADT, docetaxel, and an ARSI.
- These advances have substantially improved survival outcomes for patients with mHSPC. A recent network meta-analysis estimated that, compared to ADT monotherapy, triplet therapy is associated with a 46% decrease in mortality among patients with high-volume mHSPC.[2]
- As a consequence, collecting mature OS data from randomized controlled trials (RCTs) can require extensive follow-up, delaying patient access to new therapies. This has made surrogate endpoints such as radiographic PFS (rPFS), which can be evaluated earlier, highly appealing for clinical research.[3]
- Surrogate endpoints must be validated by establishing biological plausibility, individual-level association, and trial-level (treatment effects) association. Evaluating individual-level association typically requires access to individual patient data (IPD) from clinical trials, which can create logistical and economic challenges in establishing this important criterion.[4]
- Methods have been developed for investigating individual-level association based on published survival data. In a previous work,[5] reconstructed pseudo-IPD for rPFS and OS from digitized Kaplan-Meier curves were paired via a three-state illness-death microsimulation model, enabling survival-analytic estimation of individual-level correlations without access to IPD. Validation of predictions from the survival analytic approach against a previous surrogacy analysis utilizing actual IPD from a set of clinical studies in mHSPC[3] showed that the indirect approach produced slightly conservative surrogacy estimates compared to those obtained from IPD through bivariate Copula methods.
- Although individual-level association between rPFS and OS in mHSPC has been previously investigated,[3] the existing analyses were primarily based on older ADT studies which may no longer represent current standard of care.
- This study evaluated the individual-level association between rPFS and OS using published survival data from a contemporary list of mHSPC trials.

Objective

- To quantify the individual-level association between rPFS and OS in mHSPC using reconstructed rPFS and OS data from a contemporary evidence base.

Methods

- RCTs in mHSPC were identified through a previously published systematic review.[6]
- Unpaired pseudo-IPD for rPFS and OS were reconstructed from the RCTs,[7] then pooled separately across all arms and studies and analyzed in an illness-death model validated for estimation of individual-level association between rPFS and OS in mHSPC[5] versus a published benchmark.[3]
- Standard parametric and spline-based models were fitted to the pooled rPFS and OS pseudo IPD. Best fitting model for each outcome was selected based on statistical fit criteria and visual comparison to the observed survival and hazard trends. The extrapolated rPFS curve was adjusted to avoid crossing with extrapolated OS curve. The adjustment ensured that the weekly conditional rPFS rate did not exceed the weekly conditional OS rate across whole time horizon, to ensure clinical plausibility.
- The pre-progression death (PPD) probability and an exponentially distributed post-progression survival (PPS) curve were elicited simultaneously from the extrapolated rPFS and OS curves over a lifetime horizon (360 months [30 years]).
- PPD probability and PPS curve selection maximized concordance between the extrapolated OS curve and the indirectly modeled OS from the illness-death model.
- Paired rPFS-OS IPD were then simulated by sampling rPFS and PPS from the modeled rPFS and elicited PPS curves, respectively. Simulated rPFS and PPS durations were combined by conditioning on simulated dichotomous PPD outcomes to generate OS for each simulated patient.

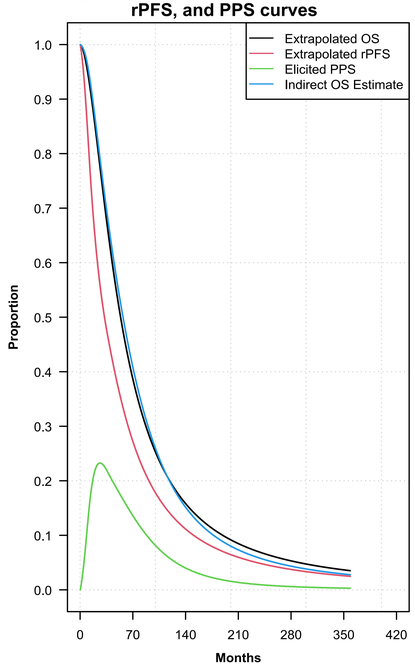
Tables and Figures

Table 1: List of clinical trials in the evidence base

Trial	Year	N	rPFS and OS Data
ARANOTE	2024	669	✓
ARASENS	2022	1305	
ARCHES	2023	1150	✓
Ayoub 2023	2023	62	
Bruun 1996	1996	140	
CALGB 90202	2014	645	
CHAARTED	2015	790	
Chang 1996	1996	92	
Chodak 1995	1995	486	
GETUG-AFU 15	2013	385	
Iversen 1996	1996	376	
Kaisary 1995	1995	304	
KEYNOTE-991	2023	1251	✓
LATITUDE	2017	1199	✓
MRC PR05	2003	311	
PEACE-1	2022	1172	✓
PROSTRATEGY	2023	150	
STAMPEDE-1	2016	1777	
STAMPEDE-5	2016	2061	
SWOG S1216	2022	1279	
SWOG S9346	2013	1535	
TITAN	2019	1052	✓
Vogelzang 1995	1995	283	
ZAPCA	2017	219	

Note: Check marks (✓) indicate studies which reported survival curves for both rPFS and OS (base case analysis). Abbreviations: N = Sample size, OS = Overall Survival, rPFS = Radiographic Progression-Free Survival.

Figure 1: Comparison of modeled OS, rPFS, and PPS curves



Abbreviations: OS = Overall Survival, PPS = Post-Progression Survival, rPFS = Radiographic Progression-Free Survival.

Table 2: Measures of association from the base case and sensitivity analyses

	Pearson's r (95% CI)	Spearman's ρ (95% CI)	Kendall's τ (95% CI)
Base case	0.958 (0.954, 0.962)	0.858 (0.848, 0.866)	0.702 (0.692, 0.712)
Study inclusion: All studies reporting curves for one or both endpoints	0.921 (0.914, 0.927)	0.818 (0.806, 0.829)	0.682 (0.670, 0.694)
PPS Hazard Rate: 10% lower	0.950 (0.946, 0.954)	0.845 (0.835, 0.855)	0.690 (0.680, 0.700)
PPS Hazard Rate: 10% higher	0.965 (0.961, 0.968)	0.871 (0.862, 0.879)	0.717 (0.708, 0.726)
PPD probability: 10% lower	0.959 (0.955, 0.962)	0.859 (0.850, 0.868)	0.704 (0.694, 0.713)
PPD probability: 10% higher	0.957 (0.954, 0.961)	0.856 (0.847, 0.865)	0.701 (0.691, 0.710)
Time Horizon: 60-months shorter	0.958 (0.954, 0.962)	0.858 (0.848, 0.866)	0.702 (0.692, 0.712)
Time Horizon: 60-months longer	0.958 (0.954, 0.962)	0.858 (0.848, 0.866)	0.702 (0.692, 0.712)
Model Choice: Second best fit*	0.953 (0.949, 0.957)	0.851 (0.841, 0.860)	0.695 (0.685, 0.705)

*Second-best fitting models for both radiographic progression-free survival and overall survival.
Abbreviations: CI = Confidence Interval, PPD = Pre-Progression Death, PPS = Post-Progression Survival.

Methods (continued)

- Correlation between rPFS and OS was measured by Pearson's *r*, Spearman's ρ, and Kendall's τ. Sensitivity of these measures was assessed with respect to model choice for rPFS and OS projections, changes in evidence base according to availability of rPFS and OS data from the RCTs, and pre-specified variations in PPD probability (±10%), hazard rate of PPS (±10%) and time horizon (±60 months) from their base case values.
- Correlation estimates were compared to those obtained from a previous individual-level surrogacy analysis in mHSPC which was conducted using actual IPD from clinical trials investigating ADT in mHSPC data. The objective for this comparison was to investigate the impact of recent changes in the treatment of mHSPC on the strength of rPFS-OS correlation.[3]

Results

- **Evidence Base**: The evidence base (**Table 1**) consisted of 24 RCTs published between 1995 and 2023, with sample sizes ranging from 62 to 2,061 and mean age ranging from 63.5 years to 72.8 years.
- Of these, seven (n=6,555) reported rPFS curves, 23 (n=18,631) reported OS curves, and six (n=6,493) reported both rPFS and OS curves.
- **Base Case Analysis Results**: Among RCTs reporting survival curves for both endpoints, the best fitting models were log logistic for OS and spline odds with two knots for rPFS.
- The estimated PPD probability was 10.2%, compared to the estimate of 45% from a previous surrogacy analysis based on IPD.[3]
- OS and rPFS curves based on the simulated IPD are presented in **Figure 1**. The predicted Pearson's *r*, Spearman's ρ, and Kendall's τ were 0.958 (95% CI: 0.954, 0.962), 0.858 (95% CI: 0.848, 0.866),and 0.702 (95% CI: 0.692, 0.712), respectively (**Table 2**). Results from this analysis represent a more conservative estimate of the individual-level correlation between rPFS and OS compared to a published benchmark [Kendall's τ: 0.83 (95% CI: 0.82, 0.84)] obtained from IPD in a prior surrogacy analysis in mHSPC.[3]
- This finding is likely attributed to the lower estimated PPD probability in the current evidence base relative to the benchmark, as reduced PPD probabilities tend to increase the divergence between rPFS and OS within the illness-death model due to positive and variable PPS (characterized by exponential distribution) for the subgroup of simulated patients who progress before death.
- **Sensitivity Analysis Results**: Across all sensitivity analyses, results were consistent with the base case analysis, with Pearson's *r*, Spearman's ρ, and Kendall's τ ranging from (0.921–0.965), (0.818–0.871), and (0.682–0.717), respectively.

Conclusions

- Consistent with previously published benchmark,[3] results from this analysis demonstrate a strong individual-level association between rPFS and OS in mHSPC. Results were consistent across a range of sensitivity analyses, indicating the stability of the results to perturbations to a selective set of key model parameters.
- Both the stability of analytical framework and the results demonstrate the utility of approaching individual-level association between rPFS-OS in mHSPC using published data. They also strengthen the case for using rPFS as a surrogate for OS to enable earlier decision-making from a clinical perspective, while reflecting the impact of changes in evidence base and mHSPC treatment landscape on this relationship.
- Strengths of the approach are its ability to leverage published Kaplan-Meier data to assess individual-level association without access to trial IPD, improving efficiency and reducing analytic burden, within a modeling framework that, compared with commonly used copula-based approaches, can generate a broader set of association metrics (including Pearson's *r*) and supports systematic sensitivity analyses across key parameters.
- A limitation of this analysis is the limited number of studies in the evidence base reporting Kaplan-Meier curves for both rPFS and OS. Additionally, the assumptions made for the tractability of the model (i.e., exponential PPS distribution) require validation using IPD from recent clinical trials or real-world settings in mHSPC for broader generalizability of findings.

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