Radiographic Progression-free Survival (rPFS) as a Surrogate Endpoint for Overall Survival (OS) in First-line (1L) Metastatic Castration-resistant Prostate Cancer (mCRPC): A Meta-analysis and Surrogate Threshold Effect

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Objective

To evaluate the validity of rPFS as a surrogate endpoint for OS in an unselected 1L asymptomatic or mildly symptomatic mCRPC population, using methodology proposed by Germany's Institute for Quality and Efficiency in Health Care (IQWiG).

Conclusions

rPFS is correlated to and a valid surrogate for OS in 1L patients with asymptomatic or mildly symptomatic mCRPC. A statistically significant effect in OS is therefore possible for a hypothetical trial demonstrating an upper confidence limit of HR < 0.83 in rPFS.

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Background

- Several treatments are available for patients with metastatic castration-resistant prostate cancer (mCRPC) in the first-line (1L) setting.
- Overall survival (OS) is accepted as the gold standard clinical endpoint for determining the therapeutic benefit of novel treatments in oncology, but it requires long follow up, delaying the identification and incorporation of effective novel treatment paradigms into clinical practice.
- We aimed to evaluate the validity of radiographic progression-free survival (rPFS), an endpoint increasingly being used in mCRPC randomized controlled trials (RCTs), as a surrogate endpoint for OS in patients with asymptomatic or mildly symptomatic mCRPC in the 1L setting, using methods recommended by IQWiG.

Materials and Methods

SYSTEMATIC LITERATURE REVIEW

- A previously conducted SLR was updated,[1] to collect evidence from inception through August 2024.
  - Methods aligned to latest guidance from Cochrane Handbook and PRISMA statement.[2,3] Protocol was registered with PROSPERO (CRD42021283512).
- Sources included MEDLINE®, Embase, Cochrane via Ovid®, and key grey literature sources.
- RCTs of available therapies for 1L mCRPC were included if they reported relative treatment effects for both rPFS and OS, either in the form of hazard ratios (HRs) or Kaplan-Meier (KM) curves.
- A rigorous feasibility assessment was undertaken to determine the presence of clinical heterogeneity across trials.

SURROGACY ANALYSIS FOR rPFS

- Assessment of surrogacy was based on methodological guidance from IQWiG.[4]
- Trial-level associations between rPFS and OS were measured using bivariate random-effects meta-analysis (BRMA) and weighted linear regression (WLR).[5,6,7] The validity of the BRMA model was assessed by using leave-one-out cross-validation (LOOCV).[5]
- The strength of the correlation estimates was assessed according to IQWiG criteria.[4] The surrogate threshold effect (STE) was calculated as needed to draw conclusions on surrogacy.
  - The STE is the minimum absolute value of the effect on the surrogate which has to be observed in a new trial to deduce an effect on the clinical endpoint.
  - In the current context, STE represents the maximum value of the HR for rPFS needed to predict a significant effect on OS.
- The following analyses were performed:
  - Primary Analysis: all trials meeting the proportional hazards (PH) assumption.
  - Sensitivity Analysis 1: all identified trials, regardless of meeting the PH assumption.
  - Sensitivity Analysis 2: excluded trial(s) that violated the PH assumption and trial(s) identified as outliers based on visual inspection. Outliers were defined as trials falling outside the 95% confidence interval (CI) in the scatterplot of log HR values for rPFS and OS.

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Results

- Eleven Phase 3 RCTs (n = 9,927 patients) were identified that met the eligibility criteria (**Table 1**).
- The primary analysis included 10 RCTs (n = 9,481) that jointly reported rPFS and OS and met the PH assumption. One trial (PEACE-3) was excluded due to PH violation.
- Sensitivity analysis 1 included all 11 RCTs (n = 9,927), while sensitivity analysis 2 excluded PEACE-3 and two visual outliers (NCT02294461 and ERA 223), resulting in 8 RCTs (n = 8,287).
- Across all analyses, BRMA and WLR models consistently indicated a medium-to-high correlation between rPFS and OS per IQWiG criteria.
  - R^2 (95% CI) for WLR: Primary: 0.65 (0.40, 0.90) (medium; **Figure 1A**); Sensitivity 1: 0.61 (0.35, 0.87) (medium; **Figure 2A**); Sensitivity 2: 0.91 (0.84, 0.99) (high; **Figure 3A**).
  - R^2 (95% CI) for BRMA: Primary: 0.78 (0.53, 0.90) (medium; **Figure 1B**); Sensitivity 1: 0.69 (0.39, 0.87) (medium; **Figure 2B**); Sensitivity 2: 0.92 (0.74, 0.97) (high; **Figure 3B**).
- STE values were 0.83 (Primary; **Figure 1A**) and 0.85 (sensitivity analysis 1; **Figure 2A**); STE was not required for sensitivity analysis 2 due to high correlation per IQWiG guidance.
- LOOCV alignment between observed and predicted OS HRs was 80% (primary analysis; **Figure 1B**), 82% (sensitivity analysis 1; **Figure 2B**), and 75% (sensitivity analysis 2; **Figure 3B**).

Table 1. Summary of Included Trials

Trial	Treatment	Sample Size
ACIS; NCT02257736	Apalutamide + abiraterone acetate + prednisone	492
	Placebo + abiraterone acetate + prednisone	490
Alliance A031201; NCT01949337	Enzalutamide	657
	Enzalutamide + abiraterone acetate + prednisone	654
COU-AA-302; NCT00887198	Abiraterone acetate + prednisone	546
	Placebo + prednisone	542
ERA 223; NCT02043678	Radium-223 + abiraterone acetate + prednisone/prednisolone	401
	Placebo + abiraterone acetate + prednisone/prednisolone	405
IPATential150; NCT03072238	Ipatasertib + abiraterone acetate + prednisone	547
	Placebo + abiraterone acetate + prednisone	554
KEYNOTE-641; NCT03834493	Pembrolizumab + enzalutamide	245 *
	Placebo + enzalutamide	242 *
NCT02294461	Enzalutamide	198
	Placebo	190
PEACE-3; NCT02194842	Radium-223 + enzalutamide	222
	Enzalutamide	224
PREVAIL; NCT01212991	Enzalutamide	872
	Placebo	845
PROpel; NCT03732820	Olaparib + abiraterone acetate + prednisone/prednisolone	399
	Placebo + abiraterone acetate + prednisone/prednisolone	397
TALAPRO-2; NCT03395197	Talazoparib + enzalutamide	402
	Placebo + enzalutamide	403

*The subgroup of patients who had not received prior abiraterone acetate was selected to align with the 1L mCRPC population of interest.

Figure 1. Primary Analysis: (A) WLR Correlation Plot and (B) BRMA LOOCV

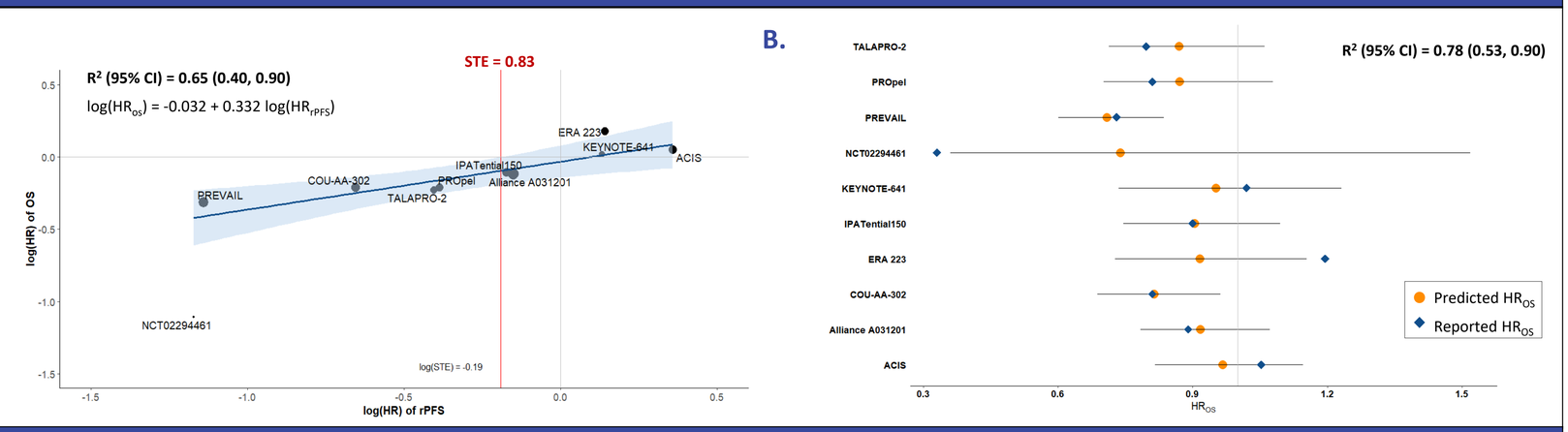


Figure 2. Sensitivity 1: (A) WLR Correlation Plot and (B) BRMA LOOCV

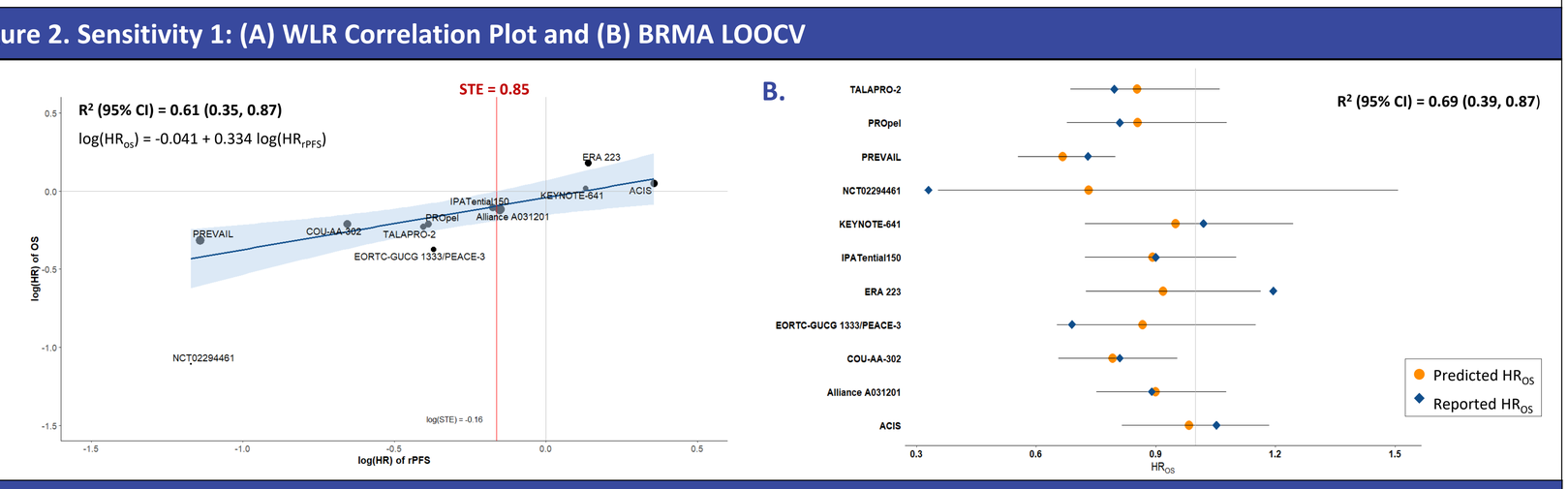
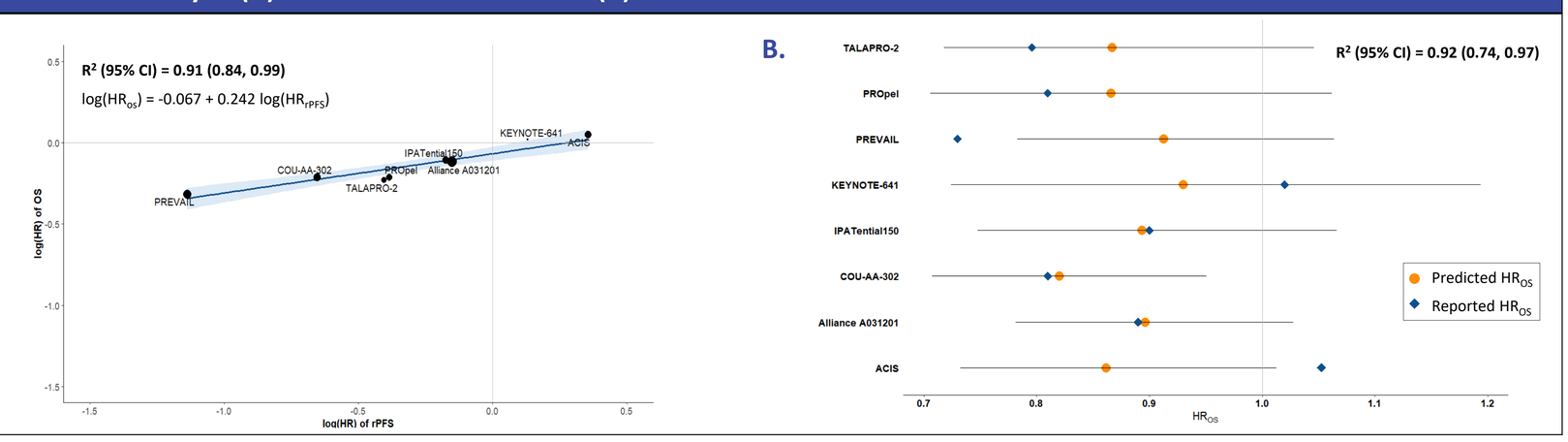


Figure 3. Sensitivity 2: (A) WLR Correlation Plot and (B) BRMA LOOCV



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Abbreviations: BRMA; bivariate random-effects meta-analysis; CI; confidence interval; HR; hazard ratio; IQWiG; Germany's Institute for Quality and Efficiency in Health Care; KM; Kaplan–Meier; LOOCV; leave-one-out cross-validation; mCRPC; metastatic castration-resistant prostate cancer; mg; milligram; kBq; kilobecquerel; kg; kilogram; OS; overall survival; PH; proportional hazards; rPFS; radiographic progression-free survival; RCT; randomized controlled trial; SLR; systematic literature review; STE; surrogate threshold effect; WLR; weighted linear regression; 1L; first-line.

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