Progression-Free Survival as a Surrogate for Overall Survival in the Front-Line Maintenance Setting for Advanced Ovarian Cancer: A Trial-Level Meta-Analysis

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Introduction and objectives

- Ovarian cancer (OC) is a leading cause of cancer-related mortality in women,[1] with ~80% of cases diagnosed at an advanced stage due to asymptomatic early disease and ineffective screening[2]
- Despite therapeutic advances, a high unmet need remains in the front-line setting for advanced OC
- While maintenance therapies have improved treatment options, to date, no front-line treatments have demonstrated a statistically significant benefit on overall survival (OS) in advanced OC trials
- Assessing OS in advanced OC trials is challenging due to the biological complexity of the disease, prolonged follow-up requirements, and post-progression treatments that may obscure the direct effects of front-line therapies. Given these challenges, progression-free survival (PFS) is commonly used as a primary efficacy endpoint in OC trials to inform clinical and regulatory decisions
- The strength of the PFS-OS surrogacy relationship in the front-line maintenance setting for advanced OC remains uncertain. This study evaluated PFS as a surrogate for OS using a systematic literature review (SLR) and meta-analysis

Materials and methods

SLR

- An SLR was conducted across MEDLINE, Embase, Cochrane databases, Northern Light Life Sciences Conference Abstracts, and the Database of Abstracts of Reviews of Effects to identify clinical trials in advanced OC. Systematic reviews and meta-analyses were included to ensure a comprehensive assessment of published evidence
- The search included full-text publications (database inception–April 18, 2024) and conference abstracts (January 1, 2017–April 18, 2024)
- Eligible publications included randomized controlled trials (RCTs) of adult patients with advanced (Stage III/IV) OC that reported both PFS and OS in either the front-line treatment setting or front-line maintenance setting. While the SLR evaluated both settings, this poster specifically focuses on the front-line maintenance setting
- Risk of bias was assessed for trials contributing to the primary analysis using the Cochrane Handbook for Systematic Reviews of Interventions[3]

Statistical analysis

- Trial-level surrogacy analysis
  - The association between treatment effects on PFS (hazard ratio [HR] for PFS) and OS (HR for OS) was assessed using weighted linear regression, with ln(HR) for OS as the dependent variable and ln(HR) for PFS as the independent variable, weighted by trial sample size
  - Surrogacy was evaluated using the correlation coefficient (R) and coefficient of determination (R^2), with good surrogacy defined as $|R| \geq 0.8$ or $R^2 \geq 0.65$[4]
  - The surrogate threshold effect (STE) for PFS was estimated as the minimum PFS benefit required to predict a statistically significant OS benefit (HR <1) in future trials
  - Model robustness was assessed via leave-one-out cross-validation, comparing predicted and observed HRs for OS within 95% prediction intervals (PIs)
  - Influential trials, defined by a Cook's distance value exceeding 3 times the mean across all trials,[5] were excluded from the main analysis and evaluated in a sensitivity analysis
- Subgroup and sensitivity analyses
  - A subgroup analysis assessed PFS-OS surrogacy in HRD-negative tumors
  - Two sensitivity analyses were conducted to (1) evaluate the impact of excluded influential trials and (2) test the robustness of findings to variations in PFS definitions

Limitations

- This meta-analysis relied on aggregate data rather than individual patient data (IPD), which, while often infeasible to obtain, would allow for patient-level correlation assessments and adjustments for measurement error, improving precision and robustness
- Variability in PFS definitions across trials introduced heterogeneity, and the sensitivity analysis using a standardized, progression-based PFS definition was restricted to 3 trials, limiting interpretability
- The small number of eligible trials limited the scope and precision of subgroup and sensitivity analyses. Additional trials are needed to strengthen the evidence base and improve generalizability

Conclusions

- This study provides up-to-date evidence of a strong trial-level association between PFS and OS in the front-line maintenance setting for advanced OC
- Findings support PFS as a potential surrogate for OS in the front-line maintenance setting, enabling earlier efficacy assessments and potentially supporting healthcare decision-making
- Further validation with larger sample sizes, standardized PFS definitions, and data from trials evaluating emerging therapies will be critical to strengthening the surrogacy relationship in an evolving treatment landscape

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Disclosures

Lei Chen, Karin Yamada, and Mehmet Burcu are employees of Merck & Co., Inc., Rahway, NJ, USA.

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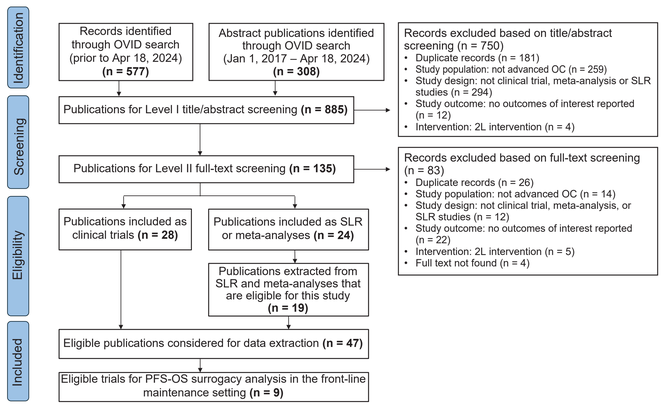
Results

Study selection and trial characteristics

- A total of 885 publications were identified from the SLR, with 9 trials meeting eligibility criteria for PFS-OS surrogacy analyses in the front-line maintenance setting (**Figure 1**)
- Eligible trials, conducted between 2006 and 2023, spanned multiple regions (1 in the US, 1 in Asia, 3 in multiple regions, and 4 with unreported locations) and included sample sizes ranging from 44 to 888 patients (**Table 1**)
- Of the 9 trials, 1 (OV-12) was identified as highly influential (Cook's distance: 0.29 vs a mean value of 0.07 across trials) and was excluded from the primary analysis. It was instead assessed in a sensitivity analysis (**Table 2**), leaving 8 trials in the primary analysis
- The risk of bias assessment supported the robustness of the findings, with 6 of 8 trials (75%) rated as having a low overall risk-of-bias and none classified as high risk (**Table 1**)

Figure 1. PRISMA flow diagram of included and excluded studies in the SLR



Trial-level surrogacy

- Eight RCTs (9 treatment comparisons, N=4,792) were included in the primary analysis of the PFS-OS surrogacy relationship
- A strong linear association was observed between treatment effects on PFS and OS (R=0.91, 95% CI: 0.75–0.98; R^2 =0.83, 95% CI: 0.56–0.97). The STE, based on a mean sample size of 532, was 0.54, indicating that a PFS HR ≤0.54 would predict a significant OS benefit in future trials (**Figure 2**)
- Cross-validation confirmed model robustness, with observed and predicted OS HRs directionally consistent in 89% of comparisons and observed HRs for OS falling within the 95% PI in 89% of cases (**Figure 3**)

Subgroup and sensitivity analyses

- In HRD-negative tumors, the PFS-OS surrogacy relationship remained consistent with the main analysis (R^2=0.84, 95% CI: 0.83–1.00; **Table 2**)
- Including the OV-12 trial weakened the surrogacy association, with R^2 dropping from 0.83 to 0.48, underscoring its influence as an outlier (**Table 2**)
- Restricting the analysis to 3 trials that explicitly defined PFS as the earliest event of progression or death resulted in a weaker surrogacy association with wider confidence intervals (R^2=0.64, 95% CI: 0.00–1.00; **Table 2**)

Figure 2. Trial-level association between PFS and OS in the front-line maintenance setting

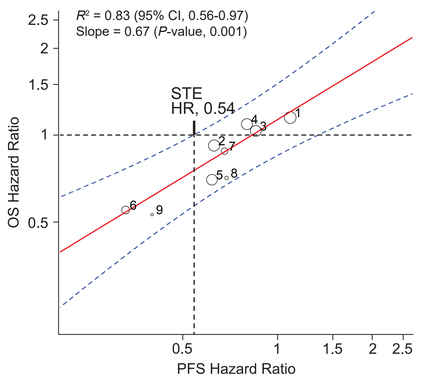
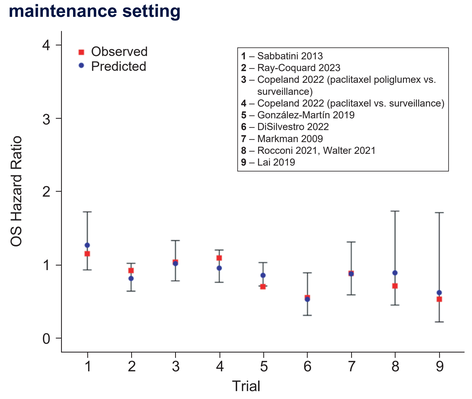


Figure 3. Cross-validation of the trial-level association between PFS and OS in the front-line maintenance setting



Notes: 1. Each circle represents a treatment comparison, with size proportional to trial sample size. 2. The red line shows the weighted linear regression of OS HRs on PFS HRs, with the blue dashed lines indicating the 95% PI. 3. The STE for PFS HR of 0.54 was based on a mean trial sample size of 532.

Note: The observed HRs for OS for each comparison are plotted against their corresponding predicted HRs and 95% PIs calculated from a weighted linear regression model with leave-one-out validation.

Abbreviations: HR, hazard ratio; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PI, prediction interval; SLR, systematic literature review; STE, surrogate threshold effect.

Table 1. Characteristics of studies included in surrogacy analyses between PFS and OS in the front-line maintenance setting

Study ID	Author and year (trial name)	Geographic region	Intervention/ comparator	Sample size	Overall risk of bias[1]
1	Sabbatini, 2013 (MIMOSA)	Not reported	Abagovomab	593	Low risk
			Placebo	295	
2	Ray-Coquard, 2023 (PAOLA-1/ENGOT-ov25)	Europe and Japan	Olaparib + bevacizumab	537	Low risk
			Placebo + bevacizumab	269	
3, 4	Copeland, 2022 (GOG-212)	Not reported	Paclitaxel poliglumex	387	Low risk
			Paclitaxel	384	
			Surveillance	386	
5	González-Martín, 2019 (PRIMA/ENGOT-OV26/ GOG-3012)	North America, Western Europe, Eastern Europe	Niraparib	487	Low risk
			Placebo	246	
6	DiSilvestro, 2022 (SOLO1/GOG-3004)	Italy, South Korea, Spain, Australia, Russia, United Kingdom, France, the Netherlands, US, Poland, Israel, Japan, China, Brazil	Olaparib	260	Low risk
			Placebo	131	
7	Markman, 2009 (SWOG-9701/GOG-178)	Not reported	12 monthly cycles of paclitaxel	150	Some concerns
			3 monthly cycles of paclitaxel	146	
8	Rocconi, 2021; Walter, 2021 (VITAL)	US	Vigil	47	Some concerns
			Placebo	44	
9	Lai, 2019 (AGOG06-001)	Taiwan	Pegylated liposomal doxorubicin + carboplatin	23	Low risk
			Observation	21	
10	Hirte, 2006 (OV-12)	Not reported	Tanomastat	122	NA[1]
			Placebo	121	

Note: 1. Risk of bias was only assessed for trials included in the main analysis.

Table 2. Subgroup and sensitivity analyses for the trial-level association between PFS and OS in the front-line maintenance setting

	Number of trials	Number of treatment comparisons	R (95% CI)	R^2 (95% CI)
Subgroup analysis in HRD-negative tumors	4	4	0.92 (0.91 – 1.00)	0.84 (0.83 – 1.00)
Sensitivity analysis including OV-12 trial (Hirte, 2006)	9	10	0.69 (0.09 – 0.97)	0.48 (0.01 – 0.94)
Sensitivity analysis in trials defining PFS as earliest of disease progression or death	3	3	0.80 (0.00 – 1.00)	0.64 (0.00 – 1.00)

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