Association Between Progression-Free Survival and Overall Survival Among Individuals Receiving First-Line Treatment for BRCA Wild-Type Advanced Epithelial Ovarian Cancer: A Patient-Level Analysis of Pooled Historical Clinical Trials

Poster Code: CO66

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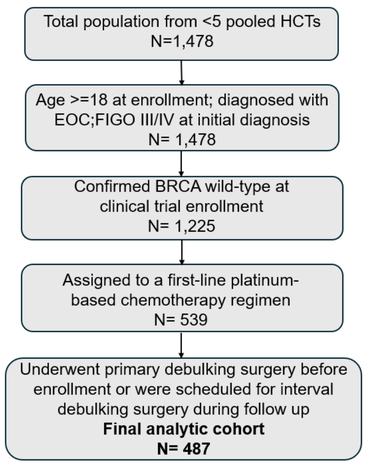
Background

- Progression-free survival (PFS) is a common primary endpoint in first-line advanced epithelial ovarian cancer (EOC) clinical trials; however, its relationship with overall survival (OS) remains uncertain.
- Evidence on the relationship between PFS and OS in advanced EOC has been inconsistent, partly reflecting underlying molecular heterogeneity, underscoring the need to evaluate surrogacy within a narrowly defined clinical context.
- This study evaluated the patient-level PFS-OS association among individuals with BRCA wild-type (wt) advanced (FIGO-stage III/IV) EOC treated with first-line platinum-based chemotherapy (PBC).

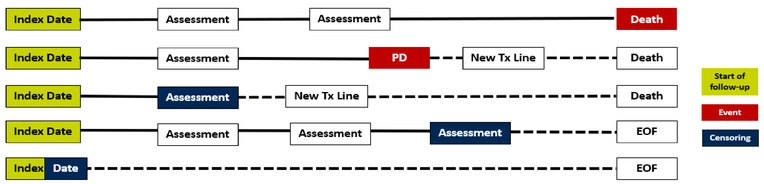
Methods

Figure 1. Patient Attrition Flow Diagram



- This retrospective study used secondary patient-level data from pooled historical clinical trials (HCTs) obtained from the Medidata Enterprise Data Store/Medidata Clinical Cloud.
- Eligible trials were interventional 1L EOC studies initiated on or after Jan 1, 2012, with primary completion on or before Dec 31, 2024, that included a PBC treatment arm, reported both PFS and OS as primary/secondary endpoints, enrolled patients with confirmed FIGO stage III/IV, documented BRCA status in eCRFs, and were covered under Medidata data-sharing agreements. (A total of <5 trials were identified and selected for analysis).
- Index Date: The date of the initiation of first-line chemotherapy on trial.
- PFS was defined as the time from the index date to the earliest occurrence of documented progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or death from any cause (**Figure 2**).

Figure 2. Definition of Progression-Free Survival



- PFS and OS were estimated using Kaplan-Meier (KM) methods. The PFS-OS correlation was assessed using restricted Spearman rank correlation, adapted for right-censored data, with sensitivity analyses using alternative correlation measures for robustness of the estimate.
- Landmark (LM) analyses were conducted at prespecified 9-, 12-, 15-, and 18-month post-index timepoints, with 15 months as primary. At each landmark, univariable and multivariable Cox models assessed the association between PFS status (PFS ≥ LM vs. PFS < LM) and subsequent OS. KM methods estimated OS from the landmark stratified by PFS status, with the log-rank test comparing survival distributions.
- Likelihood ratio tests were used to assess whether the association between 15-month PFS status and OS varied across prespecified subgroups.

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Results

- The study cohort included 487 patients who met all patient-level inclusion criteria, with a median length of follow-up of 3.4 years (IQR, 2.7) from the index date. (**Table 1**)
- Median PFS and OS from index were 15.6 months (95% CI, 13.8–16.8) and 42.1 months (95% CI 37.8-45.7), respectively. (**Figure 3 & 4**)
- The PFS-OS Restricted Spearman's correlation (ρ) was 0.7 (95% CI 0.6-0.8). (**Table 2**)
- At the prespecified 15-month landmark (**Figure 5**), the unadjusted hazard ratio (HR) for OS associated with PFS ≥15 (vs PFS <15) was 0.29 (95% CI, 0.22–0.37); sensitivity analyses at other landmark timepoints showed consistent results. (**Table 3**)
- The association between PFS and OS remained after covariate adjustment and did not vary by best overall response, bevacizumab use, or surgical type or outcome.

Table 1. Demographic and Clinical Characteristics

Characteristic	All (N=487) N (%)
Age at index (years), median (IQR)	65.0 (14)
Age ≥ 65 years	244 (50.1%)
Race	
White	439 (90.1%)
Black or African American	17 (3.5%)
Asian	11 (2.3%)
Other or Unknown	20 (4.1%)
Ethnicity	
Hispanic or Latino	20 (4.1%)
Not Hispanic or Latino	444 (91.2%)
Unknown/Missing	23 (4.7%)
Primary Tumor Site	
Ovary	375 (77.0%)
Fallopian Tube	60 (12.3%)
Primary Peritoneal	51 (10.5%)
Unknown/Missing	1 (0.2%)
Histologic Classification	
Serous	434 (89.1%)
Clear Cell	17 (3.5%)
Endometrioid	5 (1.0%)
Other or Unknown	31 (6.4%)
FIGO Stage at Diagnosis	
III	310 (63.7%)
IV	177 (36.3%)
ECOG Performance Status	
0	266 (54.6%)
1	221 (45.4%)
Surgical approaches	
Primary debulking surgery	182 (37.3%)
Interval debulking surgery (IDS)	258 (53.0%)
Planned IDS without surgery	47 (9.7%)
Chemotherapy Regimen at Index [a]	
Carboplatin + Paclitaxel	258 (53.0%)
Carboplatin + Paclitaxel + Bevacizumab	229 (47.0%)
Maintenance Therapy Type	
None	154 (31.6%)
Bevacizumab	85 (17.5%)
PARPi	124 (25.5%)
PARPi + Bevacizumab	123 (25.3%)
Other	1 (0.2%)
First-Line Bevacizumab Use	
No Use	243 (49.9%)
Treatment Only	36 (7.4%)
Treatment + Maintenance	193 (39.6%)
Maintenance Only	15 (3.1%)

a Regimen to which a patient was randomized or assigned as part of the study protocol

Figure 3. PFS for All Patients, Measured from Index Date

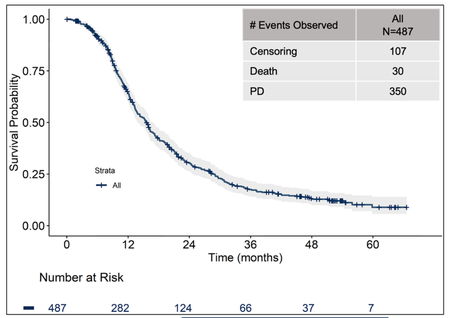

Figure 4. OS for All Patients, Measured from Index Date

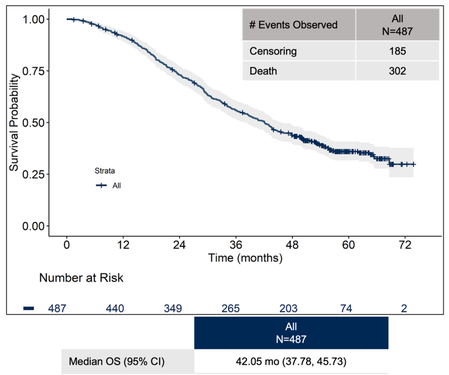

Table 2. Correlation of PFS and OS, Measured from Index Date (N = 487)

	Correlation Metric	Estimate (95% CI)
Main Analysis	Restricted Spearman's Correlation	0.70 (0.59-0.79)
Sensitivity Analysis	Highest-Rank Spearman's Correlation	0.76 (0.70-0.82)
	Normal Scores Rank Correlation	0.79 (0.75-0.83)
	Kendall's Tau [a]	0.44 (0.40-0.48)

a Kendall's Tau is based on the proportion of concordant versus discordant subject pairs and excludes pairs with indeterminate ordering under censoring, thus typically yielding more conservative (i.e., smaller) numerical values

Figure 5. OS by PFS Status at the 15-Month LM Timepoint

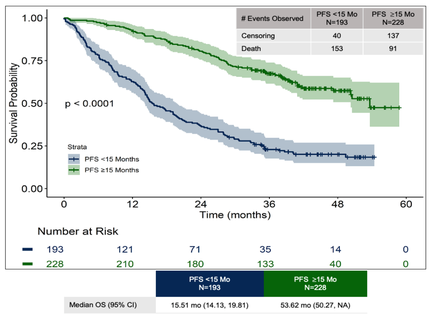

Table 3. Cox Regression Analyses for Overall Survival at Each Landmark Timepoint

	Landmark (LM) Analysis			
	9 Month (n = 455)	12 Month (n = 440)	15 Month (n = 421)	18 Month (n = 397)
Patients with PFS ≥ LM, n (%)	353 (77.6%)	283 (64.3%)	228 (54.2%)	181 (45.6%)
Unadjusted HR (95% CI) for PFS Status at Landmark (Reference: PFS < LM)	0.48 (0.37, 0.62)	0.34 (0.26, 0.43)	0.29 (0.22, 0.37)	0.26 (0.19, 0.35)
Adjusted HR (95% CI) for PFS Status at Landmark (Reference: PFS < LM) [a]	0.53 (0.40, 0.71)	0.35 (0.28, 0.46)	0.29 (0.22, 0.38)	0.26 (0.19, 0.35)

a Adjusted HRs for PFS status at landmark were obtained from models selected using bidirectional stepwise selection (using a p-value threshold of 0.20 for both entry and retention). Candidate baseline variables for stepwise selection included age at index, FIGO stage at diagnosis, ECOG closest to and prior to the landmark, primary tumor site, histologic type, residual disease after debulking, BOR to 1L therapy, bevacizumab use by landmark, and maintenance therapy use by landmark.

Limitation

- Limitations include unmeasured or residual confounding in multivariable modeling, potential misclassification of PFS status at the landmark timepoint due to variability in assessment timing or interpretation, and selection bias that may be introduced when conditioning on survival to the landmark timepoint, which may lead to a landmark cohort that is systematically different from the full trial population, potentially limiting the representativeness and generalizability of the results.

Conclusion

- In this pooled analysis of patients with BRCAwt advanced EOC receiving first-line platinum-based chemotherapy in HCTs, PFS showed a moderate patient-level association with OS.
- This association was consistent across analytic methods, was evident at all assessed landmark time points, and persisted after adjustment for key clinical covariates and across levels of hypothesized effect modifiers.
- While these findings strengthen the rationale for the use of PFS in first-line BRCAwt oncology trials, formal validation will require assessment of trial-level surrogacy across a greater number of randomized studies.

References

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