Evaluation of Surrogate Endpoints for Overall Survival in Platinum-Resistant/Refractory Ovarian Cancer

Poster #CO161

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Background

- Approximately 20% of patients with ovarian cancer progress within six months after completing platinum-based chemotherapy.[1] Various interventions have been investigated for this platinum-resistant ovarian cancer (PROC) population. It is essential to understand as early as possible whether an investigational therapy provides any survival benefits.
- Overall survival (OS) has been regarded as the standard primary endpoint in trials investigating treatments for patients with ovarian cancer. Patients can receive multiple treatments in subsequent lines of therapy, which can confound and dilute the effects of the investigated therapy on OS. Progression-free survival (PFS) and the rate of response to therapy can be determined earlier and can potentially be used as surrogates for OS in certain circumstances.
- Previous research focusing on randomized controlled trials (RCT) in first-line early ovarian cancer showed a moderate correlation in the relative treatment effect between PFS and OS.[2] It is unclear whether the same observation can be made for the PROC population.

Objective

- The objective was to assess whether PFS and the objective response rate (ORR) may be considered surrogate endpoints for OS in patients with PROC.

Methods

Trial data extraction

- A systematic literature review (SLR) of RCTs in PROC published between 2010 and April 2022 was conducted using Cytel's LiveSLR™ platform in line with the requirements of the National Institute for Health and Care Excellence (2022) and Cochrane methodology.
- Trials reporting PFS, OS, and ORR and corresponding error estimates were used in a surrogate endpoint validation in alignment with health technology assessment (HTA) guidelines, particularly the Institute for Quality and Efficiency in Healthcare (IQWiG). The ratio of ORR for the intervention vs comparators was calculated (RR_{ORR}).

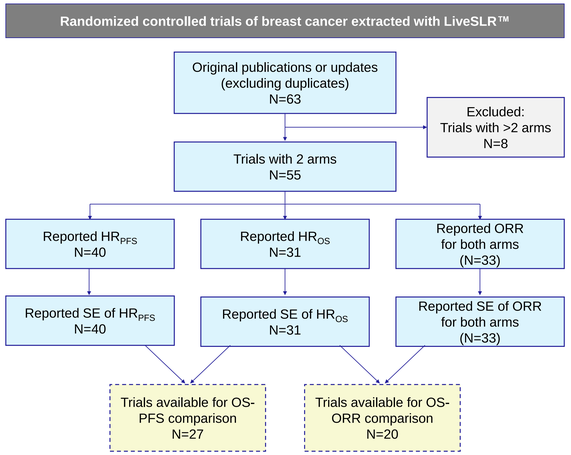
Endpoint validation

- Endpoint validation aimed to establish the magnitude of the effect on the surrogate endpoint and the association between the surrogate and final endpoint.
- Data transformations were applied to each hazard ratio (HR) endpoint ($-\ln(HR_{OS})$ and $-\ln(HR_{PFS})$) to obtain approximately normal and linear distributions of the data and to aid the interpretation of the findings.
- The pooled estimate of the effect on the surrogate was obtained from a random-effects inverse variance model with DerSimonian-Laird estimate of tau-squared. Models were fitted separately for each surrogate endpoint using trial-level point estimates and associated standard errors.
- The association between the surrogate and final endpoint was estimated using Pearson correlations.
- The surrogate threshold effect (STE) reflects the minimum treatment effect on the surrogate required to predict a non-zero effect on the final endpoint. The STE was calculated as the point at which the lower bound of the 95% confidence interval (CI) of the correlation intersects the x-axis.

Results

- In total, 63 RCTs were identified in the SLR (Figure 1). Trials with more than two arms were excluded to simplify the analysis, leaving 55 two-arm RCTs.
- Twenty-seven trials were available for OS-PFS comparison, and 20 trials were available for OS-ORR comparison.

Figure 1. Evaluation of SLR-selected studies for inclusion in the surrogate endpoints analysis



Abbreviations: HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SE, standard error; SLR, systematic literature review

- A significant pooled treatment effect on $-\ln(HR_{PFS})$ was observed (0.12, 95% CI 0.01, 0.22) indicating a significantly decreased hazard for progression in the intervention group vs the comparator group (Table 1).
- There was a significant pooled treatment effect on RR_{ORR} (1.39, 95% CI 1.2, 1.58) indicating a significantly increased ORR in the intervention group vs the comparator group (Table 1).

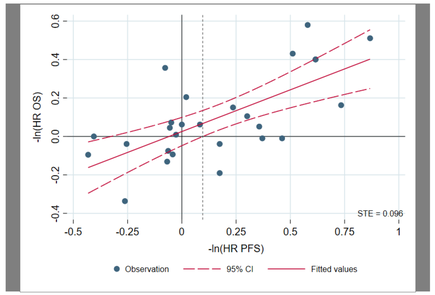
Table 1. Magnitude of effect on the surrogate endpoint

Endpoint	N	Pooled treatment effect	95% CI	80% CI	I^2 (%)
$-\ln(HR_{PFS})$	27	0.14	0.01, 0.26	0.06, 0.22	79.6
RR_{ORR}	20	1.34	1.08, 1.60	1.17, 1.51	75.2

Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; RR, relative risk

- A moderate significant correlation was observed between HR_{OS} and HR_{PFS} (r=0.68, p=0.001), with an STE of 0.096 (Figure 2, Table 2).

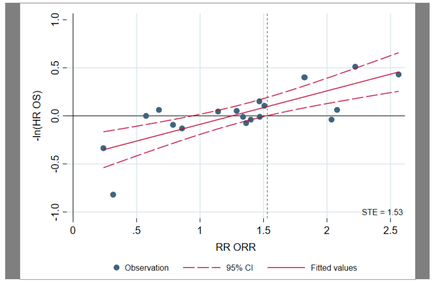
Figure 2. Correlation of $-\ln(HR_{OS})$ and $-\ln(HR_{PFS})$ and the surrogate threshold effect



Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

- A moderate significant correlation was observed between HR_{OS} and RR_{ORR} (r=0.76, p<0.0001), with an STE of 1.53 (Figure 3, Table 2).

Figure 3. Correlation of $-\ln(HR_{OS})$ and RR_{ORR} and the surrogate threshold effect



Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, relative risk; STE, surrogate treatment effect

Table 2. Association between OS and candidate surrogate PFS and ORR

Candidate surrogate endpoint	N	r (95% CI)	p-value	STE
$-\ln(HR_{PFS})$	27	0.68 (0.39, 0.84)	0.0001	0.096
RR_{ORR}	20	0.76 (0.47, 0.90)	0.0001	1.53

Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; RR, relative risk; STE, surrogate treatment effect

Discussion

- According to the IQWIG guidelines, a strong correlation is indicated by a correlation coefficient R≥0.85. A moderate correlation between OS and PFS and between OS and ORR was observed in this analysis.
- The correlation coefficient was higher for ORR-OS association compared to the PFS-OS association.
- Following the same guideline, an effect on the patient-relevant endpoint may exist when the 80% CI of the effect on the surrogate is larger than the surrogate threshold effect.
- For the PFS-OS association, neither the 95% nor 80% CI lower bound of the treatment effect on HR_{PFS} was greater than the STE (0.096), indicating no evidence of an effect on the patient-relevant endpoint and no evidence for surrogacy.
- For the ORR-OS association, neither the 95% nor 80% CI lower bound of the treatment effect on RR_{ORR} was greater than the STE, indicating no evidence of an effect on the patient-relevant endpoint and no evidence for surrogacy.

Strengths

- Studies included in this analysis were identified through a comprehensive and rigorous methodology.

Limitations

- The analysis may have been confounded by different factors such as potential post-progression therapies that may influence the OS.

Conclusion

- There was insufficient evidence to support PFS or ORR as surrogate endpoints for OS in PROC.
- Further analyses are required to explore correlations between PFS or ORR and OS within specific subgroups, such as specific treatment classes to account for mechanism of action, or by trial duration to account for time effects.

References

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