Health Technology Assessment–Relevant Validation of Progression-Free Survival as a Surrogate for Overall Survival in First-Line Metastatic Triple-Negative Breast Cancer: A Bayesian Meta-Analytic Framework

HTA337

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CONCLUSIONS

- Progression-free survival (PFS) is a reliable surrogate endpoint for overall survival (OS) in frontline metastatic triple-negative breast cancer (mTNBC)
- A comprehensive surrogate validation framework integrating trial-level, patient-level, and predictive validation approaches provided consistent evidence supporting PFS as a surrogate for OS in frontline mTNBC
- An HR_{PFS}=0.81 was identified as the surrogate threshold effect suggesting the minimum level of PFS benefit necessary to predict a statistically significant OS benefit
- These findings support the use of PFS to estimate OS benefits in future frontline mTNBC trials, including studies with crossover/treatment switch designs, helping mitigate uncertainty when OS results may be diluted

PLAIN LANGUAGE SUMMARY

- In patients being treated for metastatic triple-negative breast cancer for the first time, treatments that help patients live longer without their cancer worsening also help patients live longer overall
- This relationship remained consistent irrespective of patients receiving additional treatments after their cancer deteriorates
- The model suggested that a sufficiently large improvement in progression-free survival was needed to predict a statistically significant improvement in overall survival.
- These findings support using progression-free survival as an early indicator of long-term treatment benefit when overall survival results are not yet available

INTRODUCTION

- Overall survival (OS) remains the gold standard oncology endpoint, but its interpretation can be complicated by treatment crossover and subsequent therapies that may dilute observed survival benefits
- Progression-free survival (PFS) is less affected by post-progression treatment changes and may provide an earlier indication of clinical benefit, making it a potential surrogate for OS
- Given crossover may mask the benefit of a treatment demonstrating prolongation of OS, establishing the relationship between PFS and OS is important for clinical, reimbursement, and HTA decision-making
- Previous surrogacy evidence in metastatic triple-negative breast cancer (mTNBC) has been limited, creating a need for a more comprehensive evaluation using contemporary data

OBJECTIVE

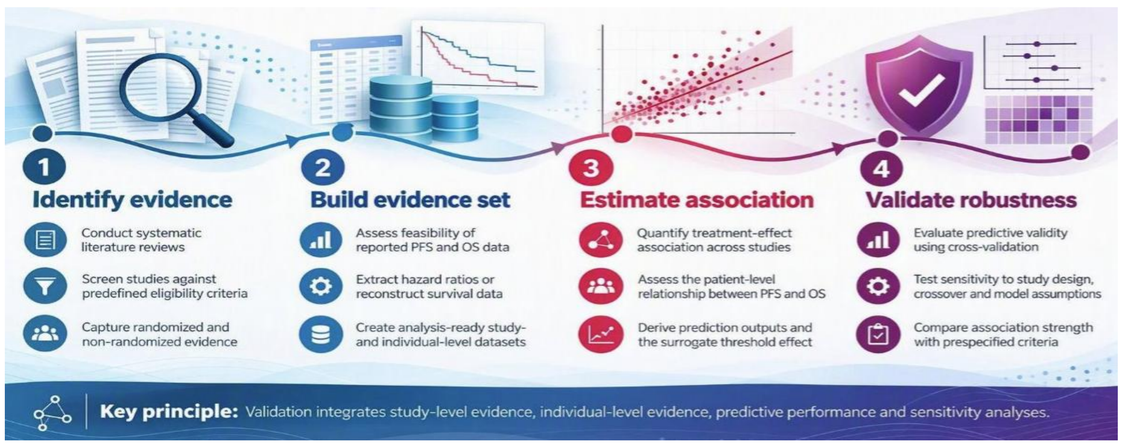
- This study evaluated whether PFS can serve as a valid surrogate endpoint for OS in frontline mTNBC through a comprehensive systematic literature review and correlation meta-analysis assessing both trial-level and patient-level associations

METHODS

Search Strategy and Inclusion Criteria

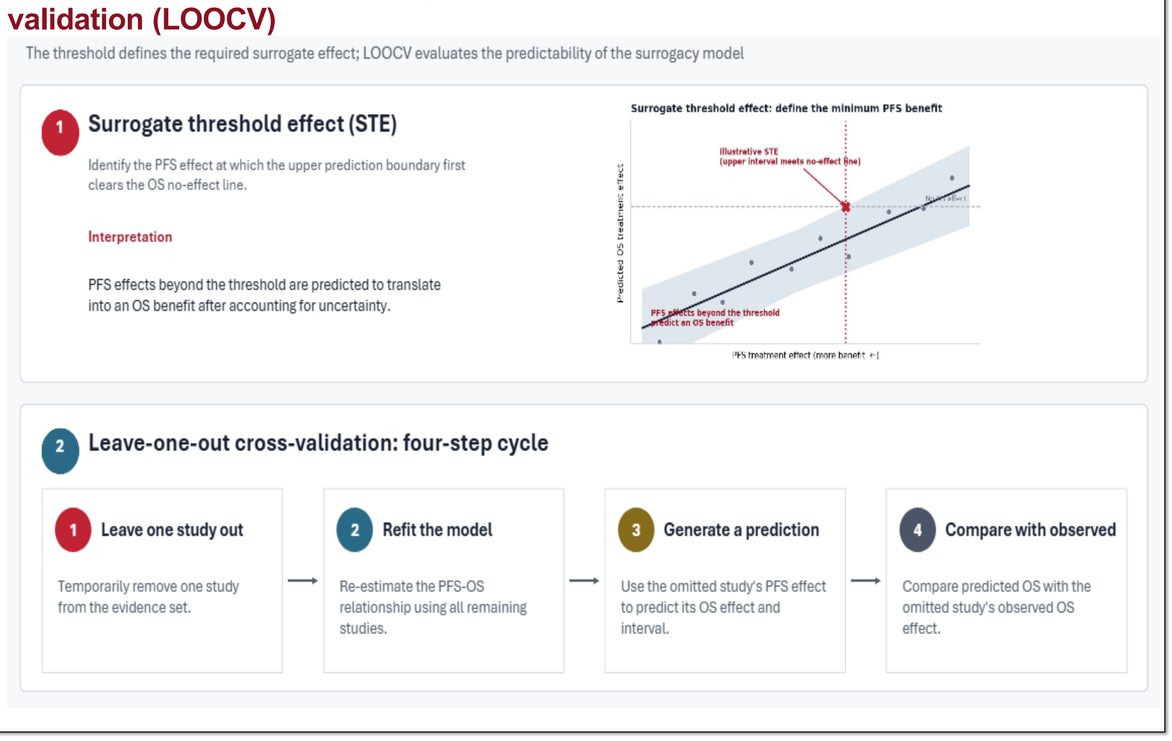
- A systematic literature review (SLR) was conducted including randomized (SLR #1) and non-randomized studies (SLR #2) in previously untreated mTNBC to identify evidence reporting PFS and/OS
- Trial-level surrogacy was determined using a Bayesian trivariate random-effects meta-analysis to quantify the association between treatment effects on PFS and OS across studies with PD-L1+ fraction as a covariate
- Individual-level association was ascertained by reconstructing pseudo individual patient data from digitized Kaplan-Meier curves, pairing the OS and PFS data using simulation methods, and estimating the relationship between PFS and OS using Pearson's correlation
- Sensitivity analyses were performed by excluding: (a) crossover/treatment switch studies (b) paired single-arm studies (c) non-RCTs, (d) studies violating proportional hazard assumption
- Predictive ability of the model was further ascertained using (a) surrogacy threshold effect (b) leave-one-out cross-validation
- Our approach to evidence identification for surrogate validation and determination of surrogacy threshold estimate/leave-one-out-cross-validation are further illustrated in Figure 1 and 2, respectively

Figure 1. Methodology: From evidence identification to surrogate validation



Crossover is a form of treatment switching in which patients randomized to the control arm receive all or part of the experimental regimen in a subsequent line of therapy. Built-in crossover is prospectively enabled by the trial protocol upon meeting predefined conditions, whereas switching to the standard-of-care occurs post-progression as part of routine care and is driven by treatment availability rather than trial design. Both may confound interpretation of OS and subsequent HTA assessment

Figure 2. Method steps: Surrogate threshold estimate and leave-one-out-cross-validation (LOOCV)

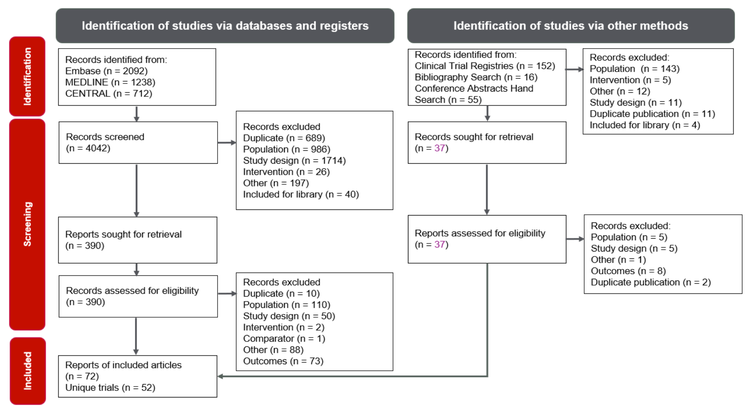


- Sensitivity analyses were conducted for the trial-level and individual-level analyses
- STE and LOOCV evaluations were also repeated for the sensitivity analyses
- Strength of correlation was ascertained using published thresholds and HTA guidance

RESULTS

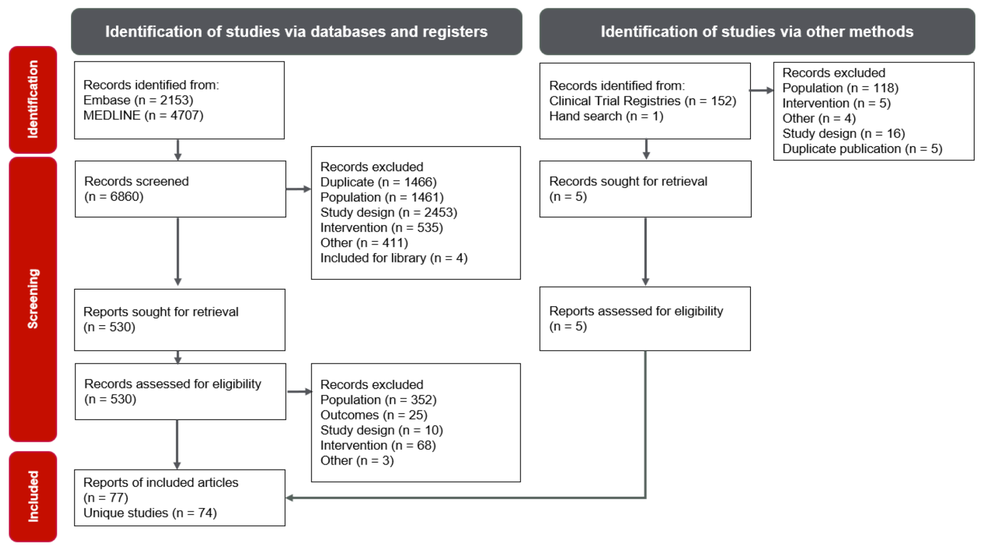
- The SLR screened >11,000 abstracts and included 149 publications across both RCT and non-RCT evidence base
- 52 studies (56 treatment comparisons) were identified, including RCTs, observational studies, and crossover/treatment switch studies (n=7; 1 study design, 6 SOC)
- 32 comparisons reported both PFS and OS, while 11 comparisons reported PFS, OS, and PD-L1 status, enabling robust surrogacy analyses

Figure 3. PRISMA flow diagram for SLR #1



n: Number of records, PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses, SLR: Systematic Literature Review.

Figure 4. PRISMA flow diagram for SLR #2



n: Number of records, PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses, SLR: Systematic Literature Review.

PFS–OS SURROGACY ANALYSIS | 1L mTNBC

Primary and sensitivity analyses support consistent PFS–OS surrogacy findings

Trial-level treatment-effect associations remained strong; individual-level Pearson correlations from the simulation method were generally moderate in all-comer analyses.

TRIAL-LEVEL SURROGACY — Primary: all-comers — Pearson r **0.87**

INDIVIDUAL-LEVEL SURROGACY — Primary: all-comers — Pearson r **0.63**

	TRIAL-LEVEL SURROGACY				INDIVIDUAL-LEVEL SURROGACY		
Analysis set	N	Pearson r (95% CrI)	R^2 (95% CrI)	STE	LOOCV coverage	N	Pearson r, simulation (95% CI)	Interpretation
Primary: all-comers	52	0.87 (0.71, 0.94)	0.76 (0.50, 0.89)	0.81	100%	34	0.63 (0.61, 0.66)	Moderate
Excluding crossover studies	45	0.90 (0.79, 0.96)	0.81 (0.62, 0.92)	0.76	100%	29	0.66 (0.64, 0.68)	Moderate
Excluding non-RCTs	43	0.81 (0.53, 0.92)	0.66 (0.28, 0.85)	0.80	100%	27	0.63 (0.61, 0.65)	Moderate
Excluding paired single-arm studies	50	0.86 (0.68, 0.94)	0.74 (0.47, 0.88)	0.80	100%	32	0.62 (0.60, 0.64)	Moderate
Excluding HRs violating PH assumption	46	0.82 (0.58, 0.93)	0.68 (0.34, 0.86)	0.81	100%	28	0.62 (0.59, 0.65)	Moderate
PD-L1− subgroup	–	–	–	–	–	9	0.51 (0.47, 0.54)	Moderate
PD-L1+ subgroup	–	–	–	–	–	9	**0.94 (0.93, 0.95)**	Very strong

CrI, credible interval; CI, confidence interval; IO, immunotherapy; LOOCV, leave-one-out cross-validation; PH, proportional hazards; RCT, randomized controlled trial; STE, surrogate threshold effect.

Median crossover/treatment switch rate from comparator to all/part of intervention agent in the subsequent line of setting = 35.8%. Primary analysis enables OS prediction from PFS in 1L mTNBC trials with little or no crossover/treatment switch

STRENGTHS AND LIMITATIONS

- Large evidence base: Largest PFS–OS surrogacy analysis in TNBC to date, substantially expanding the evidence available for evaluation
- Comprehensive validation: Evaluated surrogacy at both the study and individual-patient levels, addressing two key dimensions of surrogate validity
- Robust methodology: Used a trivariate random-effects meta-analysis and extensive sensitivity analyses, with broadly consistent findings across study-design assumptions
- Limited PD-L1 data: Incomplete reporting of PD-L1 status resulted in poor convergence of PD-L1-related model parameters in the primary analysis
- Reconstructed patient-level data: Individual-level analyses relied on data derived from published survival curves, and the simulation assumption that PFS and post-progression survival were unassociated may have conservatively estimated PFS–OS correlation

References

1. Zhuang SH, et al. Cancer J. 2009;15:395-400.
2. Bujkiewicz S, et al. Value Health. 2026 Feb 10:S1098-3015(26)00050-1. doi: 10.1016/j.jval.2026.01.020.
3. CDA-AMC, et al. Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment. Available at https://www.cda-amc.ca/sites/default/files/MG%20Methods/surrogateendpoints-report.pdf.

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Disclosures

AD and AK are employees of Gilead Sciences, Inc., and hold stock with Gilead Sciences, Inc. PS, GN, and DP are employees of Evidinno Outcomes Research Inc. All authors contributed to draft development and final approval.