https://doi.org/10.29289/259453942025V35S1028

Progression-free survival as a surrogate endpoint for overall survival in antibody-drug conjugate trials for advanced breast cancer: a systematic review and meta-analysis

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Objective: To evaluate the validity of progression-free survival (PFS) as a surrogate endpoint for overall survival (OS) in randomized controlled trials assessing antibody-drug conjugates in advanced breast cancer. **Methods:** A systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Searches were conducted on PubMed, Embase, and Cochrane databases, including conference proceedings up to February 2024. Linear regression models weighted by trial size assessed trial-level correlation between hazard ratios for PFS and OS. Surrogacy strength was classified based on the coefficient of determination (R^2): strong (≥0.7), moderate (0.5–0.69), or weak (<0.5). **Results:** Fifteen randomized controlled trials involving 7,360 patients were included. Overall, a moderate correlation between PFS and OS was identified (R^2=0.61; 95% confidence interval [CI] 0.29–0.94). Subgroup analyses revealed variability, with a notably weak correlation in human epidermal growth factor receptor-type 2 (HER2)-positive breast cancer (R^2=0.31; 95%CI 0.00–1.00). Trials with fewer participants (≤529) exhibited stronger correlations (R^2=0.74; 95%CI 0.35–1.00) compared to larger studies (>529 participants; R^2=0.36; 95%CI 0.00–1.00). The surrogate threshold effect for meaningful OS prediction was identified as a 25% reduction in the hazard ratio for PFS across trials. **Conclusion:** PFS showed moderate surrogacy for OS in antibody-drug conjugate trials for advanced breast cancer, with substantial variation across subgroups. Given the weak correlation in HER2-positive disease, reliance solely on PFS might misrepresent true clinical benefit. OS should remain the primary endpoint in trials evaluating antibody-drug conjugate efficacy.

Keywords: breast cancer; immunoconjugates; meta-analysis.