Individual Participant Data Meta-Analysis for Time to Event Outcomes: One-Stage or Two-Stage Method?

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CONCLUSIONS

- The one-stage and two-stage models used in this Individual Participant Data (IPD) meta-analysis effectively captured and validated treatment effects
- For a nuanced analysis, the one-stage approach is preferable for IPD meta-analyses of fewer studies. In contrast, the two-stage approach is better for meta-analyses with large number of studies in the presence of heterogeneity
- Where possible, both one-stage and two-stage approaches should be used to leverage their complementary strengths for time-to-event analysis

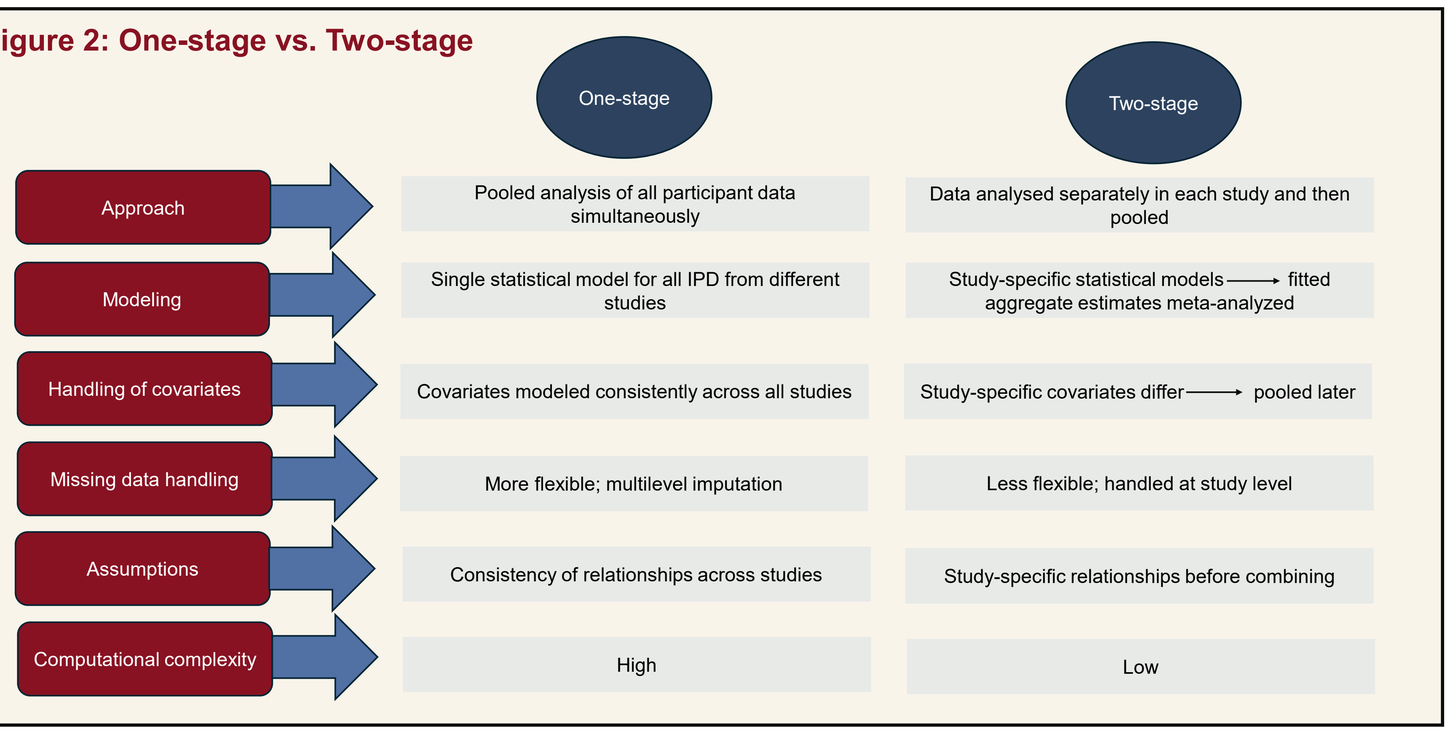
PLAIN LANGUAGE SUMMARY

- One-stage approach analyzes all participant data in a single unified statistical model, best for fewer trials
- Two-stage approach assesses each study separately using descriptive analysis, then combines results, ideal for meta-analyses of large number of studies with heterogeneity
- The intervention showed statistically significant improvements in all the outcomes including overall survival, progression-free survival, and time to deterioration compared to the comparator
- Both methods produced consistent results, confirming their effectiveness and robustness in estimating treatment effects

INTRODUCTION

- Individual Participant Data (IPD) meta-analysis is widely regarded as the gold standard in evidence synthesis compared to aggregate data meta-analysis due to its enhanced accuracy and flexibility[1]
- Unlike traditional aggregate data meta-analyses, IPD meta-analysis utilizes raw, individual-level data from multiple studies, allowing for precise estimation of treatment effects and subgroup analyses[2]
- Despite numerous comparisons, there is still some uncertainty regarding when to employ the one-stage versus the two-stage approach in IPD meta-analysis[3]
- The meta-analysis conducted using IPD involves mainly two methods including one-stage and two-stage
- A one-stage IPD meta-analysis involves pooling and evaluating patient-level data from multiple clinical trials, whereas the two-stage IPD meta-analysis is typically employed when the individual-level data from multiple studies are analyzed separately in each study, and then combined in a second stage to generate an overall estimate[2,4]

Figure 2: One-stage vs. Two-stage



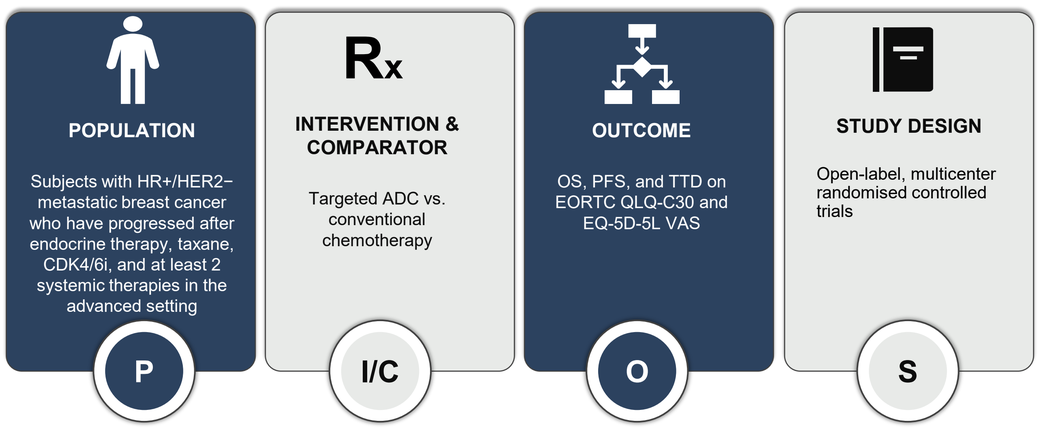
OBJECTIVE

- The current study compares one and two-stage IPD meta-analysis methods to assess the effectiveness of treatments on time-to-event (TTE) outcomes

METHODS

- This study utilized one-stage and two-stage meta-analysis techniques to process IPD from phase 3 trials in metastatic breast cancer, evaluating overall survival (OS), progression-free survival (PFS), and time-to-deterioration (TTD) on European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) and EuroQol 5 Dimensions (EQ-5D) instruments
- **Figure 1** depicts the pre-defined eligibility criteria for the meta-analysis

Figure 1 : PICOS criteria for inclusion in the meta-analysis



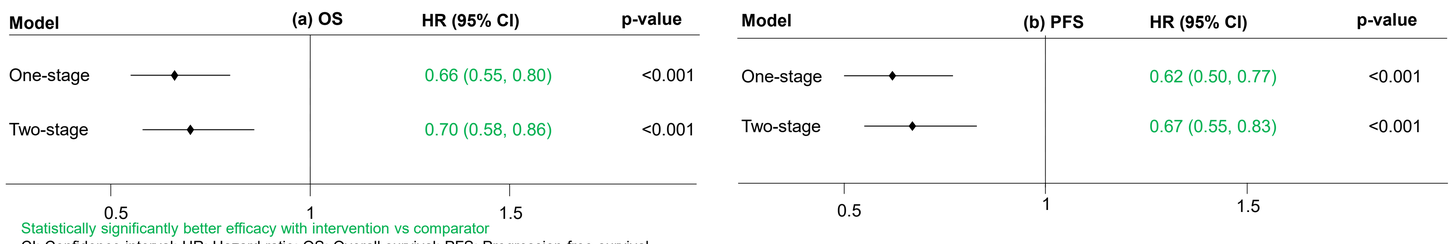
ADC: Antibody-drug conjugate; CDK4/6i: CDK4/6 inhibitor; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D-5L VAS: EuroQol Five Dimensions Five Levels Visual Analogue Scale; HER2-: Human epidermal growth factor receptor 2 negative; HR+: Hormone receptor-positive; OS: Overall survival; PFS: Progression-free survival; TTD: Time to deterioration

- Hazard ratios and 95% confidence interval (CI) were estimated for survival and TTE outcomes using a stratified Cox proportional hazards regression analysis
- TTD assessment was performed in the EORTC QLQ-C30 and EQ-5D-5L evaluable population, which was defined as intention-to-treat (ITT) subjects who completed at least one domain/dimension at baseline and had at least one evaluable assessment post-baseline
- The one-stage meta-analysis pooled IPD data from two studies into a single unified statistical model, adjusting for clinically and statistically relevant covariates
- The two-stage IPD meta-analysis analyzed each study separately with relevant covariates and then pooled the summarized results
- **Figure 2** demonstrates the major differences between one-stage and two-stage model in terms of approach, modeling, covariate and missing data handling, assumptions and computational complexity

RESULTS

- Both one-stage and two-stage models consistently estimated treatment effects on OS and PFS, favoring the intervention (**Figure 3**)
- Similar findings were also reported for TTD on EORTC QLQ-C30 and EQ-5D scale after including death (death as event), which favored the intervention versus the comparator (**Figure 4**)
- The one-stage IPD meta-analysis was chosen as the base-case due to the limited number of studies in the analysis
- The alignment of both models, directionally and statistically, highlighted the reliability and robustness of the estimates

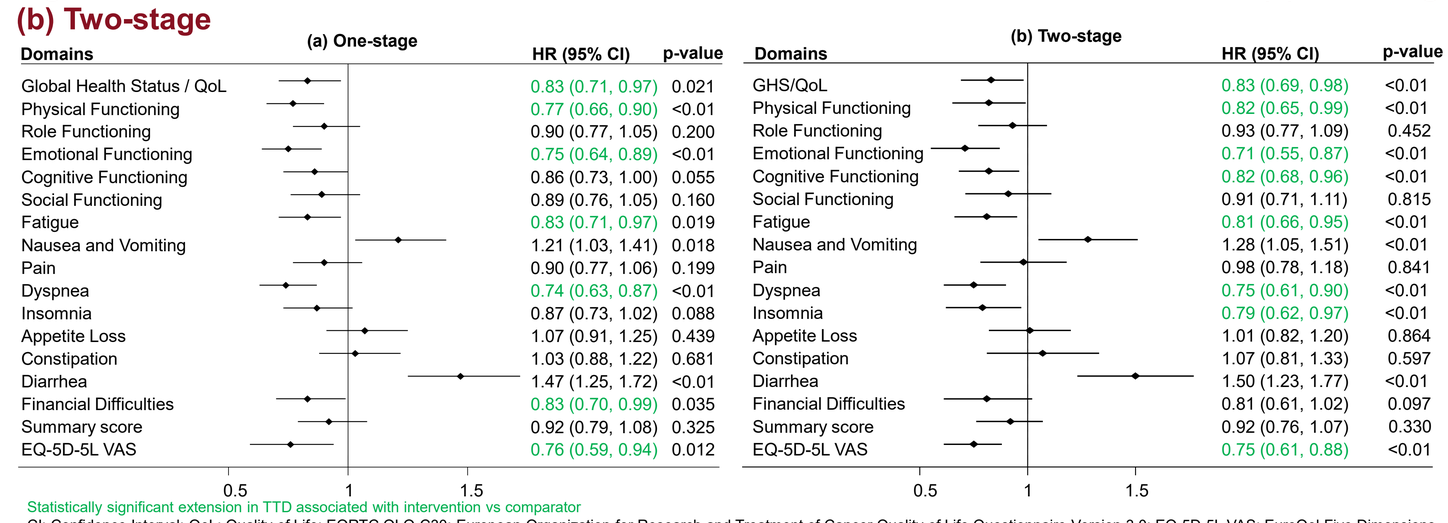
Figure 3 : One-stage and two-stage results for (a) Overall survival with intervention vs. comparator (b) Progression-free survival with intervention vs. comparator



Statistically significantly better efficacy with intervention vs comparator

CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival

Figure 4: Results for TTD outcomes on EORTC-QLQ-C30* and EQ-5D-5L VAS scale: (a) One-stage (b) Two-stage**



Statistically significant extension in TTD associated with intervention vs comparator

CI: Confidence Interval; QoL: Quality of Life; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D-5L VAS: EuroQol Five Dimensions Five Levels Visual Analogue Scale; TTD: Time to Deterioration

*The 30-item EORTC QLQ-C30 questionnaire consisted of 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, nausea, and vomiting), a global health status/QOL scale (GHS/QoL), and 6 single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties). A summary score for the EORTC QLQ-C30 is also calculated as the mean of 13 out of the 15 domains, excluding the GHS/QoL and financial difficulties[4]

EQ-5D** measure includes an EQ-5D-5L scale and a visual analog scale (VAS)[4]

LIMITATIONS

- Both methods depend on the availability of individual participant data from the contributing studies, which can be challenging due to data security concerns, proprietary issues, or incomplete datasets
- Both approaches are vulnerable to publication bias if the studies included in the meta-analysis are not representative of all relevant research, such as if only studies with favorable results are published
- The findings from both one-stage and two-stage methods may be less generalizable to broader populations if the included studies focus on narrow or highly selected patient groups

References

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