EUR REV MED PHARMACOL SCI
2026; 30: 316-326

TRASTUZUMAB DERUXTECAN PLUS PERTUZUMAB AS A SUBSTANTIAL ADVANCEMENT IN PREVIOUSLY UNTREATED PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

A. MESSORI[1], T. LUPI[2], L. GASPERONI[3], L. DEL BONO[4], A. OSSATO[5], V. DAMUZZO[6,7]

[1]Osservatorio Innovazione Regione Toscana, HTA Unit, Firenze, Italy
[2]Hospital Pharmacy, Local Health Unit Lanciano Vasto, Chieti, Italy
[3]Department of Pharmaceutical, USL Toscana Centro, Prato, Italy
[4]Department of Pharmacy, University of Pisa, Pisa, Italy
[5]UOC Territorial Pharmaceutical Service, Azienda ULSS 8 Berica, Vicenza, Italy
[6]Department of Pharmacy, Vittorio Veneto Hospital, AULSS2 Marca Trevigiana, Vittorio Veneto, Italy
[7]Italian Society of Clinical Pharmacy and Therapeutics (SIFaCT), Torino, Italy

Corresponding Author
Andrea Messori, MD; e-mail: andrea.messori@osservatorioinnovazione.net

ABSTRACT – *Objective:* First-line treatment of HER2-positive metastatic breast cancer (HER2+MBC) has recently evolved with the introduction of trastuzumab deruxtecan-based regimens. We performed an indirect comparative analysis to evaluate the relative efficacy of currently available first-line treatments using reconstructed individual patient data (IPD).

Materials and Methods: A systematic PubMed search identified phase III randomized controlled trials evaluating first-line therapies for HER2+MBC with progression-free survival (PFS) reported through Kaplan-Meier curves. Reconstructed IPD were generated using the IPDfromKM method after digitization of published curves. Three trials were included: DESTINY-Breast09, EMERALD, and CLEOPATRA. Trastuzumab plus pertuzumab plus taxane (THP) was adopted as the common comparator. Treatment effects were estimated using a Cox proportional hazards model and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Heterogeneity across pooled control groups and proportional hazards assumptions were also assessed.

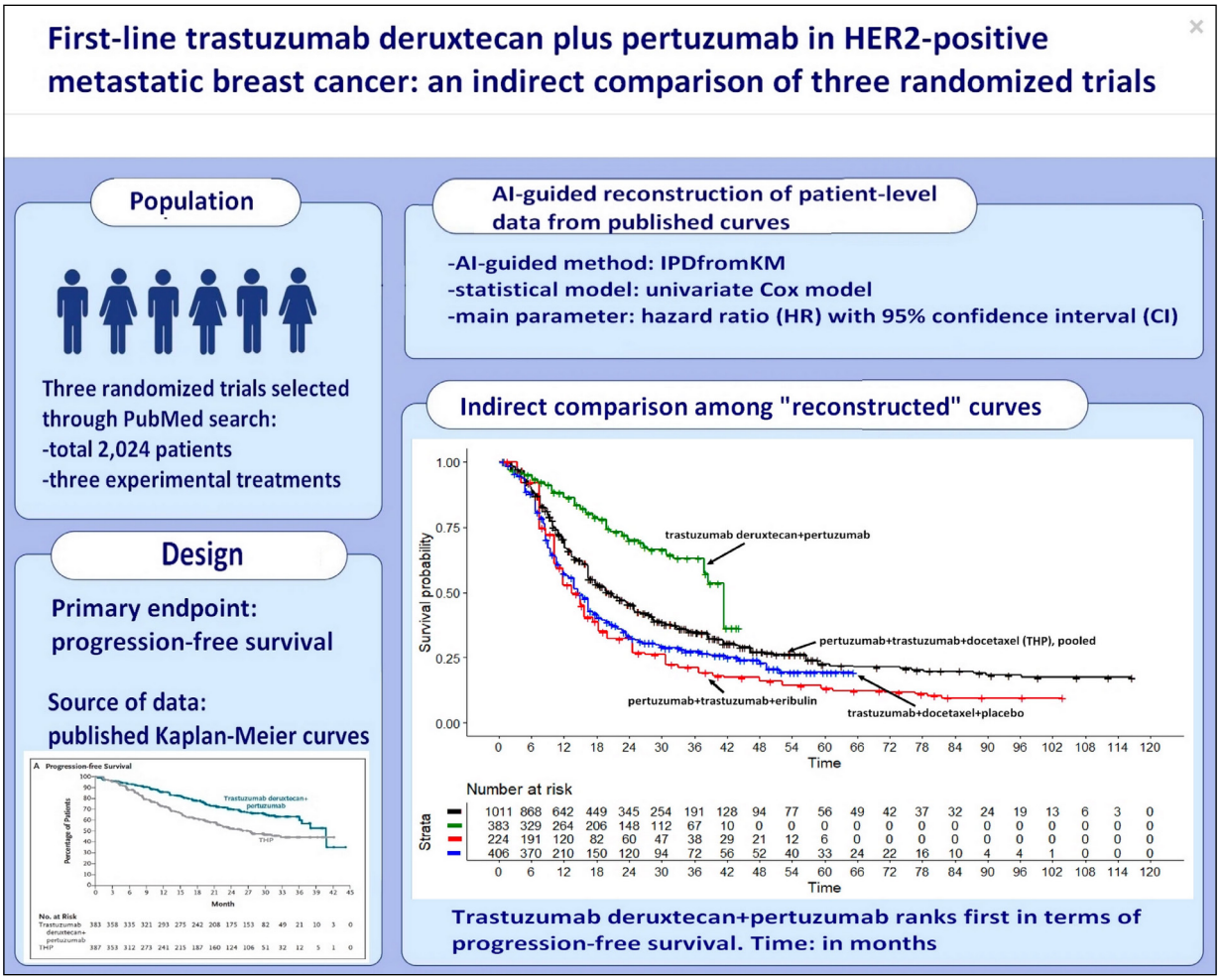
Results: The combination of trastuzumab deruxtecan plus pertuzumab demonstrated the most favorable PFS profile among the evaluated regimens. Compared with pooled THP controls, this regimen significantly reduced the event risk (HR 0.49; 95% CI 0.40 to 0.60). In contrast, trastuzumab plus pertuzumab plus eribulin showed PFS outcomes substantially overlapping with THP (HR 0.96; 95% CI 0.77 to 1.20). Reconstructed HR estimates were highly consistent with those reported in the original trials, confirming the reliability of the IPDfromKM approach.

Conclusions: Indirect comparisons based on reconstructed patient-level data suggest that trastuzumab deruxtecan plus pertuzumab currently represents the most effective first-line strategy for HER2+MBC in terms of PFS.

KEYWORDS: HER2-positive metastatic breast cancer, First-line treatments, Indirect comparisons, IPDfromKM method, Progression-free survival.

INTRODUCTION

Substantial therapeutic advancements in the treatment of HER2-positive metastatic breast cancer (HER2+MBC) have been reported in 2026. Until recently, the combination of trastuzumab, pertuzumab and a taxane (most commonly docetaxel), known as THP, was recognized as the standard of care for this condition[1-3]. However, the development of trastuzumab deruxtecan, es-



Graphical Abstract. Trastuzumab deruxtecan plus pertuzumab in HER2-positive metastatic breast cancer.

pecially when combined with pertuzumab, seems to have changed this paradigm. First, the new regimen includes only two agents, and second, very promising data from a randomized controlled trial (RCT) have recently been reported on the efficacy of this new regimen[1,4].

HER2-positive breast cancer accounts for approximately 15-20% of all breast cancer diagnoses and has historically been associated with an aggressive clinical course, characterized by rapid disease progression and reduced survival compared with HER2-negative disease[5-9]. The introduction of HER2-targeted therapies has dramatically changed the prognosis of these patients. The development of trastuzumab represented the first major breakthrough, followed by the incorporation of pertuzumab and other anti-HER2 agents that progressively improved disease control and survival outcomes. As a consequence, HER2-positive metastatic breast cancer has become one of the most successful examples of precision oncology, where treatment selection is driven by a specific molecular target and where sequential HER2-directed therapies can provide prolonged clinical benefit[10-13].

Despite these advances, the optimal first-line treatment strategy remains a matter of active investigation. The CLEOPATRA trial[14] established the combination of trastuzumab, pertuzumab and docetaxel as the reference standard, demonstrating a substantial improvement in PFS and setting a benchmark that remained largely unchanged for more than a decade. During this period, several alternative approaches were evaluated to improve efficacy, reduce chemotherapy-related toxicity, or simplify treatment administration. However, most investigational regimens were unable to demonstrate a clear survival advantage over the established THP combination.

More recently, antibody-drug conjugates have emerged as a particularly promising therapeutic class in HER2-positive disease[1,2,4]. Trastuzumab deruxtecan combines the targeting properties of trastuzumab with the cytotoxic activity of a po-

tent topoisomerase-I inhibitor payload and has shown remarkable efficacy in heavily pretreated patients. These encouraging results stimulated the investigation of trastuzumab deruxtecan in earlier treatment settings, including first-line therapy. The publication of the DESTINY-Breast09 trial[4] therefore represents a potentially paradigm-changing event because it evaluates a trastuzumab deruxtecan-based regimen in previously untreated metastatic patients and compares its outcomes with the long-standing standard of care.

Therefore, this potentially innovative, two-agent treatment deserves to be compared with other recently developed treatments for this disease condition[14,15]. Our comparative analysis was based on the IPDfromKM method[16-18], an artificial intelligence technique that first elaborates the Kaplan-Meier curves published in the trials (along with basic trial information, such as the total number of patients and events), and then uses this information to generate a database of "reconstructed patients" or "reconstructed" individual patient data (IPD). Thus, the IPDfromKM method generates an IPD database for each Kaplan-Meier curve reported in the included trials.

As these patient-level databases are independent of one another, researchers can perform any combination of binary comparisons to assess the effectiveness of treatments. This is particularly useful when a 'true' trial comparing the two treatments of interest does not exist. Over the past few years, a substantial body of literature has emerged on the application of the IPDfromKM method, particularly in oncology and cardiology, with 173 and 106 articles published in these fields between 2021 and 2025, respectively[18]. Virtually all these studies have demonstrated the excellent performance of the IPDfromKM method in reconstructing patient-level data.

MATERIALS AND METHODS

Literature search

We conducted a systematic search of the PubMed database to identify randomized controlled trials (RCTs) that were relevant to our analysis. The two main eligibility criteria were as follows: a) randomized controlled trial (RCT); b) previously untreated patients with HER2-positive metastatic breast cancer (abbreviated to HER2+MBC). The last PubMed search was performed on 26 April 2026 using the following search terms: (HER2 AND metastatic AND "breast cancer"). This search covered the entire PubMed database from 1990 onwards and was combined with a filter set to include only RCTs. This selection process adhered to the PRISMA guidelines[19]. To select the studies evaluated in our analysis, the following inclusion criteria were applied: (a) phase III RCT; (b) first-line treatment of patients with HER2+MBC; (c) combination regimen given to the treatment group (abbreviated as HER2TT) and evaluated for superiority compared with the control arm; (d) THP given to the control group (THP is an acronym for taxane + trastuzumab + pertuzumab); (e) availability of PFS outcomes; and (f) data presented through Kaplan-Meier curves. To avoid including the same patients from the same trial more than once, the most recent publication from each trial was selected. Treatment with THP for the control groups was chosen to increase the homogeneity of indirect comparisons and ensure that the so-called geometry of direct and indirect comparisons remained as simple as possible.

Reconstruction of individual patient data

As previously mentioned, the IPDfromKM method[15-17] was applied to all Kaplan-Meier curves of the treatment and control arms reported in the selected RCTs. These Kaplan-Meier curves were digitized with WebPlotDigitizer (version 4.7; https://apps.automeris.io/wpd/; accessed 1 February 2026; distance = 20, $\Delta x = 15$, $\Delta y = 15$). The extracted X–Y coordinates, together with the reported numbers of enrolled patients and events, were subsequently processed using the online version of the IPDfromKM software. Further details on the reconstruction procedure are reported in Appendix A. This approach generated reconstructed datasets containing survival times (defined as the interval from trial enrolment to the last available follow-up) and patient outcomes, categorized as alive/censored or deceased. Reconstructed IPD were obtained for each RCT arm. The entire procedure was independently performed in duplicate by two investigators, and the resulting datasets were compared for consistency to minimize the risk of manual errors.

Study design and data analysis

Our analysis aimed to evaluate the relative efficacy of first-line HER2-targeted therapies (HER2TT) for patients with HER2+MBC, with progression-free survival (PFS) as the primary endpoint. Kaplan-Meier curves for PFS were reconstructed for each trial arm. In our comparative analyses, THP was adopted as the common comparator across the included trials; in this three-drug regimen, taxane was usually docetaxel. As requested by the IPDfromKM method, in one phase of our PFS analysis we pooled the arms receiving THP across the included studies and analyzed them as a cumulative control group.

Treatment effects were estimated using a univariate Cox proportional hazards model, with the results expressed as hazard ratios (HR) and 95% confidence intervals (CI). Heterogeneity of the control groups across the trials was evaluated using likelihood ratio tests. Indirect pairwise comparisons among active regimens were performed using univariate Cox regression models based on HR.

Finally, as the Cox model is based on the assumption of proportional risk over time, we tested the extent to which this assumption was met using Schoenfeld's residual statistics[20].

An additional methodological consideration concerns the interpretation of indirect comparisons based on reconstructed patient-level data. Unlike conventional network meta-analyses that rely primarily on aggregate measures reported in publications, the IPDfromKM approach recreates individual survival trajectories and allows direct application of standard survival-analysis techniques. This feature offers important advantages because investigators can generate pooled Kaplan-Meier curves, estimate median survival times, perform proportional-hazards testing, and conduct exploratory subgroup analyses whenever sufficient information is available.

Nevertheless, reconstructed datasets do not correspond to the original trial databases and should therefore be considered approximations of the true patient-level information. The accuracy of reconstruction depends on several factors, including the quality of the published Kaplan-Meier curves, the availability of numbers at risk, the precision of the digitization process, and the completeness of reported event counts. For these reasons, reconstructed analyses are generally intended to complement rather than replace evidence derived from original patient-level datasets.

Registration

This study was registered on the Research Registry (https://www.researchregistry.com/) as a Systematic Review (date: July 22, 2026; registration code: reviewregistry2119).

RESULTS

Figure 1 summarizes the main phases of our literature search based on the PRISMA guidelines. Our search selected three RCTs. Their main characteristics are described in Table I. The regimens evaluated in the three treatment groups included: a) trastuzumab deruxtecan plus pertuzumab;

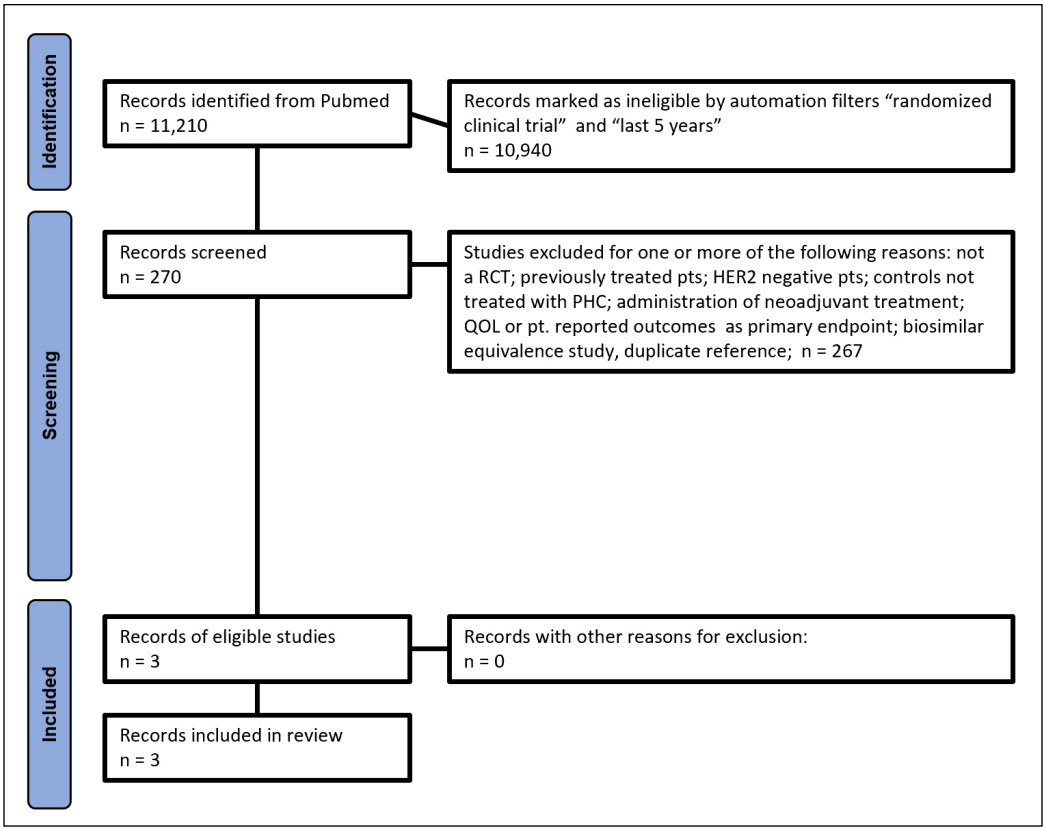


Figure 1. PubMed search according to the PRISMA guidelines.

Table I. Characteristics of the three RCTs included in our main analysis.

Trial	Patients' characteristics	Follow-up duration (months)	Experimental treatment	Taxane arm	Reference treatment	Crude event rates
DESTINY BREAST-09, 2026[4]	Patients with HER2-positive advanced or metastatic BC and no previous chemotherapy or HER2-directed therapy for metastatic disease.	42	Trastuzumab deruxtecan plus pertuzumab (n=383)	THP (n=387)	NA	T=118/383 C=172/387
EMERALD 2025[14]	Patients with HER2-positive BC cancer receiving first-line systemic treatment for locally advanced or metastatic disease.	66	Trastuzumab plus pertuzumab plus eribulin (n=224)	THP (n=222)	NA	T=159/224 C=153/222
CLEOPATRA 2020[15]	Patients with HER2-positive metastatic BC receiving placebo plus trastuzumab plus docetaxel (control group) or pertuzumab plus trastuzumab plus docetaxel pertuzumab group) as first-line treatment.	96	NA	THP (n=402)	Trastuzumab plus docetaxel plus placebo (n=406)	T=329/406 C=304/402

RCT, randomized controlled trial; BC, breast cancer; T, treatment group; C, control group; NA, not applicable; THP, trastuzumab plus pertuzumab plus taxane (docetaxel in most cases).

b) trastuzumab plus pertuzumab plus eribulin; c) trastuzumab plus docetaxel plus placebo.

Beyond the numerical estimates of HR, visual inspection of the reconstructed Kaplan-Meier curves provided additional information regarding the temporal pattern of treatment benefit. The survival curve of trastuzumab deruxtecan plus pertuzumab separated early from the pooled control group and maintained this advantage throughout the entire observation period. This pattern suggests that the benefit associated with the experimental regimen was not restricted to a specific phase of follow-up but rather reflected a durable reduction in mortality risk over time.

Another noteworthy observation concerns the magnitude of the survival difference between trastuzumab deruxtecan plus pertuzumab and the other active regimens. Whereas the survival curves of THP and trastuzumab-pertuzumab-eribulin showed substantial overlap during most of follow-up, the curve associated with trastuzumab deruxtecan plus pertuzumab remained consistently higher. The persistence of this separation supports the robustness of the treatment effect and is consistent with the favorable HR estimates obtained from the Cox analyses.

The heterogeneity analysis also generated clinically relevant information. Although the three THP control groups showed a common overall pattern, important differences were observed across studies. These differences may reflect variations in patient selection, trial conduct, subsequent therapies, and follow-up duration. Therefore, the heterogeneity detected by the likelihood-ratio test should not necessarily be interpreted as a methodological weakness but rather as a reminder that PFS outcomes are influenced by multiple factors extending beyond the experimental treatment itself.

Regarding our indirect comparisons of PFS across the treatments, Figure 2 (Panel A) shows the Kaplan-Meier curves generated by our main analysis based on reconstructed patients, while Figure 2 (Panel B) shows the results of our heterogeneity assessment based on the three control groups. The doublet regimen of trastuzumab deruxtecan + pertuzumab (N=383) showed superiority compared with the other treatments with the following values of HR: HR =0.4893 (95% CI, 0.4014 to 0.5964) *vs.* the control groups pooled (n=1,011); HR = 0.374 (95% CI, 0.287 to 0.487) *vs.* trastuzumab+docetaxel+placebo (n=224); HR = 0.343 (95% CI, 0.270 to 0.453) *vs.* pertuzumab+trastuzumab+eribulin (n=406).

The likelihood ratio test showed a significant degree of heterogeneity across the three control groups ($p<0.05$). According to the Kaplan-Meier curves of Figure 2 (Panel B), this heterogeneity seems to depend to a considerable extent on the THP arm of the CLEOPATRA trial[14], whose PFS pattern was clearly worse than that of the other two trials. By contrast, regarding the DESTINY Breast-09 trial[4], the outcomes pattern of the controls showed a particularly favorable PFS, thus contributing to determining the significant heterogeneity. Table II shows the median values

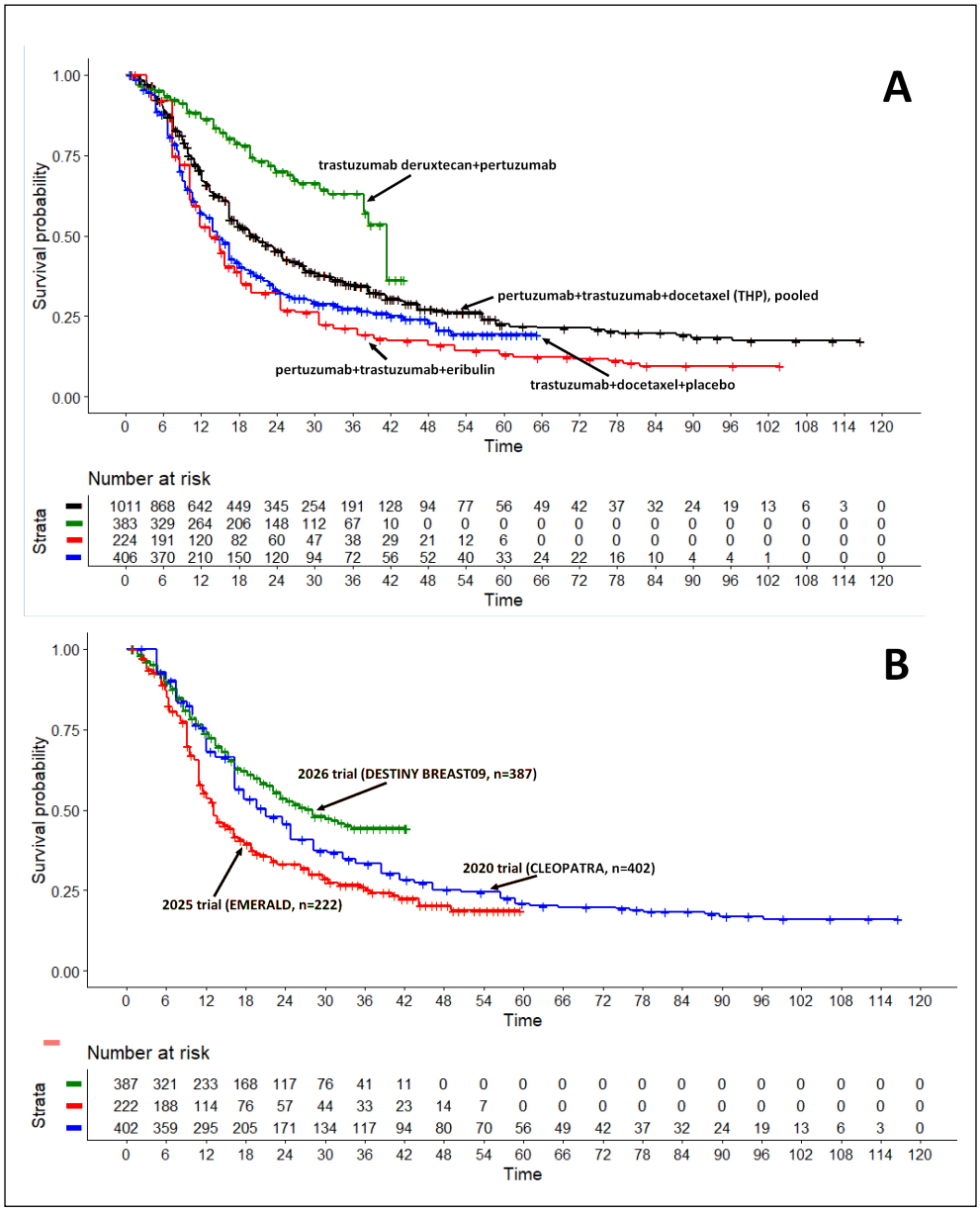


Figure 2. **A**, Main analysis. R regarding the CLEOPATRA trial, the pooled arm of 1,011 patients included the arm of 402 patients treated with THP. **B**, Heterogeneity analysis based on the three groups treated with THP. Endpoint: PFS. Time in months. THP, taxane plus trastuzumab plus pertuzumab; PFS, progression-free survival.

estimated for each arm of the three trials and the HR values for the comparison in each trial between the treatment group *vs.* the pooled control groups. On the one hand, these medians confirm the high effectiveness of the two-agent combination of trastuzumab deruxtecan plus pertuzumab; on the other, they confirm the significant heterogeneity across the three THP arms.

Regarding the Schoenfeld test (Figure 3), the data showed no significant deviation from the proportional hazards assumption (p=0.13), thus confirming the validity of the Cox model. As shown in the figure, the global line of Schoenfeld's test and the four data points representing each treatment are close to a horizontal pattern.

Finally, the last two columns of Table II indicate strong agreement between the HR from each original trial and the HR estimated from reconstructed patients (in comparison with the specific control arm of the trial). These data therefore confirm the excellent performance of the reconstruction algorithm of the IPDfromKM method.

DISCUSSION

The present analysis compared the efficacy of the main first-line treatments currently available for patients with HER2+MBC using PFS as the primary endpoint. By reconstructing IPD from published

Table II. PFS data reported in the three RCTs.

Trial	Comparator arm		Taxane arm		HR from reconstructed patients (in comparison with the three arms pooled)	HR from reconstructed patients (in comparison with the specific control arm of the trial)	HR from the original trial
	Treatment	Median with 95% CI (months)	Treatment	Median with 95% CI (months)			
DESTINY BREAST-09, 2026[4]	Trastuzumab deruxtecan plus pertuzumab (n=383)	41.4 (95% CI, 38.5 to 41.4)	THP (n=1,011, three arms pooled)	20.3 (95% CI, 18.3 to 23.2)	0.4893 (95% CI, 0.4014 to 0.5964)	0.6187 (95% CI, 0.4876 to 0.7851)	0.56 (95% CI, 0.44 to 0.71)
EMERALD, 2025[5]	Trastuzumab plus pertuzumab plus eribulin (n=224)	14.0 (95% CI, 12.8 to 17.3)		12.9 (95% CI, NR)	1.3077 (95% CI, 1.0981 to 1.5574)	0.9643 (95% CI, 0.7731 to 1.203)	0.95 (95% CI, 0.76 to 1.19)
CLEOPATRA, 2020[6]	Trastuzumab plus docetaxel plus placebo (n=406)	12.4[§] (95% CI 10 to 14)		18.7 (95% CI, 17 to 22)	1.4721 (95% CI, 1.2898 to 1.6802)	0.675 (95% CI, 0.578 to 0.788)	0.69 (95% CI, 0.59 to 0.81)

[§]The outcomes of this arm of the CLEOPATRA trial were significantly worse compared with the THP arm because in this trial THP was the experimental arm compared which was compared with the placebo arm.
THP, taxane plus trastuzumab plus pertuzumab, i.e. Taxotere+Herceptin+a taxane.

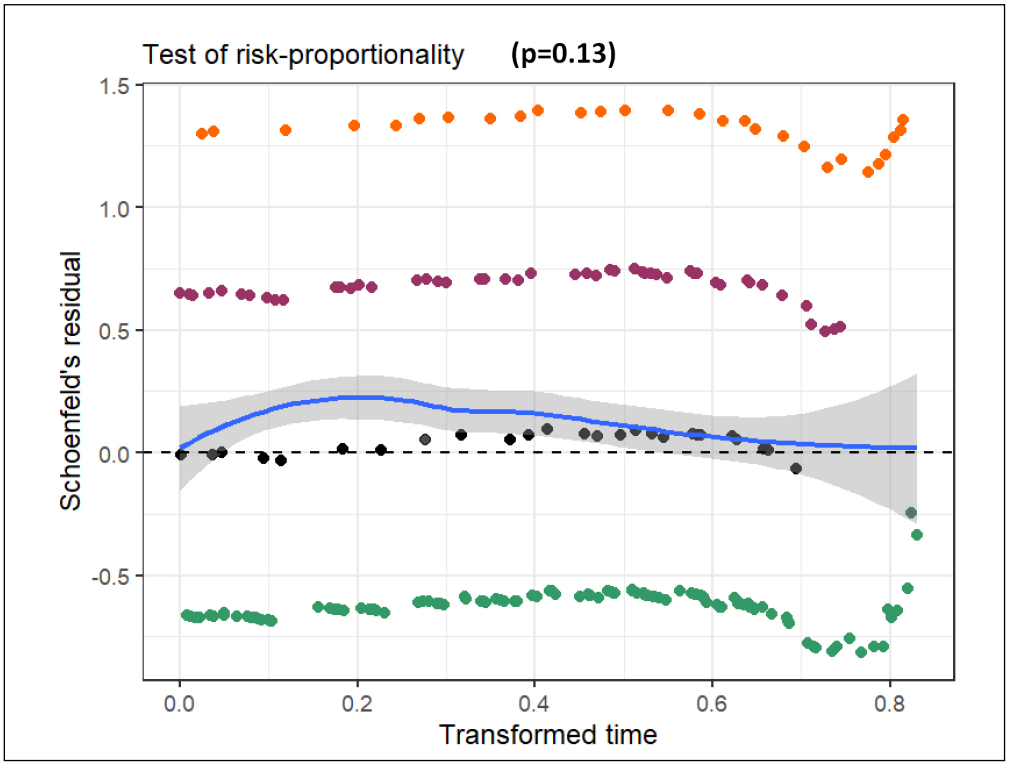


Figure 3. Schoenfeld's test to evaluate violations from risk proportionality assumption. In blue, the overall (or "global") residuals line according to Schoenfeld model (p = 0.13); in green, data points of patients treated with THP (n=1,011); in black, data points of patients treated with trastuzumab deruxtecan+pertuzumab (n=383); in red, data points of patients treated with trastuzumab+ docetaxel+placebo (n=224); in purple, data points of patients treated with pertuzumab+trastuzumab+eribulin (n=406). THP, taxane plus trastuzumab plus pertuzumab.

Kaplan-Meier curves, our study generated indirect comparisons among regimens separately evaluated in "true" randomized trials but linked through a common comparator represented by THP.

The main finding of our analysis is that the two-drug combination of trastuzumab deruxtecan plus pertuzumab showed the most favorable survival profile among the evaluated regimens. In particular, this treatment demonstrated a marked reduction in the risk of death compared with the pooled THP control groups and maintained a consistent advantage also when compared with the specific control arm of the DESTINY-Breast09 trial[4]. Notably, the HR values for trastuzumab deruxtecan plus pertuzumab were markedly better than the values of the other treatments. Likewise, the median survival of trastuzumab deruxtecan plus pertuzumab (41.4 months) was particularly long compared with the other medians (Table II). By contrast, the regimen based on trastuzumab, pertuzumab and eribulin produced survival outcomes that substantially overlapped with those of THP. This confirmed the non-inferiority profile already suggested by the EMERALD trial[15] but ruled out the possibility of superior outcomes.

From a clinical perspective, our findings support the hypothesis that trastuzumab deruxtecan combined with pertuzumab may represent a substantial advancement in the first-line treatment of HER2+MBC. Until recently, the standard paradigm of therapy in this setting was based on chemotherapy combined with dual HER2 blockade, particularly the THP regimen established by the CLEOPATRA study[14]. The DESTINY-Breast09 trial[4] introduced a potentially practice-changing strategy because the experimental regimen combined only two agents while achieving superior efficacy outcomes. This therapeutic simplification may have relevant implications not only for efficacy but also for treatment burden and long-term tolerability.

The biological rationale underlying the superiority of trastuzumab deruxtecan-based therapy deserves further consideration. Unlike conventional monoclonal antibodies, trastuzumab deruxtecan functions as an antibody-drug conjugate capable of delivering a highly potent cytotoxic payload directly to HER2-expressing tumor cells. In addition, the membrane-permeable payload may generate a so-called bystander effect, potentially contributing to antitumor activity even in neighboring cells characterized by heterogeneous HER2 expression. These mechanisms may partially explain the magnitude of benefit observed in recent clinical studies and support the hypothesis that trastuzumab deruxtecan is capable of overcoming some mechanisms of resistance associated with previous HER2-targeted therapies.

Another relevant implication of our findings concerns treatment simplification. Historically, first-line management of HER2-positive metastatic disease has relied on combinations including cytotoxic chemotherapy. Although effective, chemotherapy-based regimens are associated with cumulative toxicity, treatment discontinuations, and a substantial burden for patients. The possibility of achieving superior efficacy with a regimen composed of trastuzumab deruxtecan plus pertuzumab raises the prospect of reducing dependence on conventional chemotherapy while maintaining or even improving clinical outcomes. This aspect may be particularly relevant in patients requiring prolonged treatment exposure.

Our results should also be interpreted in the broader context of the rapidly evolving therapeutic landscape of HER2-positive breast cancer. The availability of increasingly effective HER2-directed agents has transformed metastatic disease into a condition characterized by sequential treatment opportunities. Consequently, the selection of first-line therapy may influence the effectiveness of subsequent treatment lines and the overall therapeutic trajectory of patients. Future investigations should therefore address not only the comparative efficacy of individual regimens but also the optimal sequencing strategy across the entire continuum of care.

An additional issue concerns economic sustainability. Trastuzumab deruxtecan is an innovative therapy associated with substantial acquisition costs. Although pharmacoeconomic analyses were beyond the scope of the present study, the large survival gains observed in recent trials suggest that future cost-effectiveness evaluations will be important for healthcare decision-makers. In particular, the balance between clinical benefit, treatment costs, resource utilization, and patient-reported outcomes will likely become increasingly relevant as new HER2-directed therapies enter clinical practice.

Finally, our study contributes to the growing body of literature supporting the use of reconstructed patient-level analyses as a complementary source of comparative evidence[18]. In situations where direct randomized comparisons are unavailable, these methods can provide timely information that may assist clinicians, researchers, and policy-makers in interpreting rapidly evolving evidence. Although indirect comparisons cannot replace prospective head-to-head trials, they can help identify clinically meaningful differences among treatment options and generate hypotheses for future research.

Another important aspect emerging from our study concerns the role of indirect evidence generated through reconstructed IPD. In oncology,

direct head-to-head trials comparing all clinically relevant regimens are rarely available. Consequently, comparative analyses based on IPD reconstruction have progressively gained importance as a pragmatic tool for evaluating relative treatment effects through indirect comparisons across different studies[18]. In our analysis, the strong agreement between the HRs (with CIs) reconstructed through the IPDfromKM method and those originally reported in the trials (Table II) further confirms the reliability of this methodological approach. This observation is consistent with the extensive validation literature accumulated in recent years for this technique[17,18].

The assessment of heterogeneity across the THP control groups deserves specific consideration and suggests caution in interpreting our results. The three trials differed in terms of enrolment periods, follow-up duration, and some patient characteristics, which may explain the significant cross-trial heterogeneity we found. The survival curves of the THP groups showed a certain degree of consistency overall; however, one should keep in mind the long temporal interval separating the CLEOPATRA trial from the most recent studies. Improvements in supportive care, diagnostic procedures, and subsequent treatment lines may have partially influenced PFS outcomes across the trials.

Our analysis also evaluated the proportional hazards assumption underlying the Cox model. The Schoenfeld residuals test did not show statistically significant violations, indicating that the use of HR was methodologically acceptable in this setting. This point is important because reconstructed-patient analyses based on time-to-event endpoints may occasionally be influenced by non-proportional hazards, especially in oncology studies characterized by long-term survivors.

Limitations

Some limitations of our study should be acknowledged. First, this was an indirect comparison rather than a true randomized head-to-head trial. Despite the use of a common comparator, cross-trial differences may still introduce confounding factors that cannot be completely adjusted for using reconstructed data; this is consistent with the significant level of heterogeneity that we found. Second, the IPDfromKM method generates reconstructed rather than original patient-level data; therefore, minor inaccuracies related to curve digitization and reconstruction procedures are unavoidable. Third, our analysis focused exclusively on PFS and did not evaluate other clinically relevant endpoints such as overall survival, objective response rate, toxicity, or quality of life. In particular, safety outcomes are highly relevant when comparing regimens characterized by markedly different treatment intensities and mechanisms of action. Fourth, our analysis was affected by the typical limitations intrinsic to the IPDfromKM method[16-18]; the most important one is that only univariate Cox model regression analyses can be made based on the primary endpoint, whereas multi-variate Cox models aimed at assessing covariates other than the primary endpoint cannot be employed, simply because these covariates are not available in the patient-level reconstructed database. Other limitations are related to the indirect nature of the cross-trial comparisons. On the other hand, the IPDfromKM method has the important advantage of reproducing the specific Kaplan-Meier curves for each treatment (along with their respective follow-up durations) while taking into account the timing of events' occurrence, which are two pieces of information that network meta-analysis is unable to manage. Finally, the number of available randomized trials in this specific clinical setting remains limited.

CONCLUSIONS

In conclusion, our analysis suggests that trastuzumab deruxtecan plus pertuzumab currently represents the most promising first-line therapeutic option among the regimens evaluated for HER2-positive metastatic breast cancer. The magnitude of the observed survival benefit, together with the consistency of the results across multiple comparative analyses, indicates that this treatment may represent a substantial advancement over historical standards of care.

The study also highlights the value of reconstructed patient-level methodologies for generating comparative evidence when direct randomized comparisons are unavailable. The close agreement between reconstructed and published HR estimates further supports the methodological reliability of this approach.

At the same time, the presence of cross-trial heterogeneity and the indirect nature of the comparisons require cautious interpretation. Confirmation through additional prospective evidence, longer follow-up, and real-world studies will be important to fully characterize the long-term benefits and safety profile of trastuzumab deruxtecan-based strategies. Nevertheless, the currently available evidence strongly supports the growing role of this regimen in reshaping the treatment paradigm of HER2+MBC and provides a rationale for its consideration as a new reference option in the first-line setting.

Conflict of Interest
The authors declare no conflict of interest.

Funding
The authors received no specific funding for this study.

Data Availability
Patient-level data supporting these findings are available from the authors upon request.

Ethics Approval
Not applicable due to the type of study.

Informed Consent
Not applicable.

Data Availability
The data supporting the findings of this systematic review were extracted from previously published studies, which are cited within the manuscript. No new datasets were generated.

ORCID ID
Andrea Messori: 0000-0002-5829-107X
Tiziano Lupi: 0000-0002-4587-8736
Lorenzo Gasperoni: 0000-0001-6427-0809
Luna Del Bono: 0009-0007-8094-1677
Andrea Ossato: 0000-0001-8984-4733
Vera Damuzzo: 0000-0002-3685-6789

Authors' Contributions
Andrea Messori: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration,
Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
Tiziano Lupi: Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
Lorenzo Gasperoni: Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
Luna Del Bono: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.
Andrea Ossato: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.
Vera Damuzzo: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Quaquarini E, Luelli F, Lasagna A, Rizzo G, Perrone L, Figini S, Achille R, Pedrazzoli P. Trastuzumab-Deruxtecan for the Treatment of Metastatic Breast Cancer Patients: Data from Real World Studies. Cancers (Basel) 2025; 17: 3505.
2. Kumar A, Jerzak KJ, Gelmon KA, Boileau JF, Bouganim N, Brezden-Masley C, Cao JQ, Cescon DW, Chia S, Edwards S, Joy AA, Laing K, LeVasseur N, Sehdev S, Simmons C, Webster M, Manna M, On Behalf Of Patient Advocacy Breast Cancer Canada. Guidance for Canadian Breast Cancer Practice: National Consensus Recommendations for the Systemic Treatment of Patients with HER2+ Breast Cancer in Both the Early and Metastatic Settings (2025 Update). Curr Oncol 2026; 33: 200.
3. Wei C, Zheng Q, Ma X, Sun X, Wang Z, Tang S, Liu Y, Wang X. What is the optimal first-line regimen for patients with advanced HER2-positive breast cancer: A systematic review and network meta-analysis. J Cancer Res Ther 2025; 21: 875-885.
4. Tolaney SM, Jiang Z, Zhang Q, Barroso-Sousa R, Park YH, Rimawi MF, Saura C, Schneeweiss A, Toi M, Chae YS, Kemal Y, Chaudhari M, Şendur MAN, Yamashita T, Casalnuovo M, Danso MA, Liu J, Shetty J, Herbolsheimer P, Loibl S; DESTINY-Breast09 Trial Investigators. Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2026; 394: 551-562.
5. Marra A, Chandarlapaty S, Modi S. Management of patients with advanced-stage HER2-positive breast cancer: current evidence and future perspectives. Nat Rev Clin Oncol 2024; 21: 185-202.
6. Avelino ARM, Pulipati S, Jamouss K, Bhardwaj PV. Updates in Treatment of HER2-positive Metastatic Breast Cancer. Curr Treat Options Oncol 2024; 25: 1471-1481.
7. Boscolo Bielo L, Trapani D, Nicolò E, Valenza C, Guidi L, Belli C, Kotteas E, Marra A, Prat A, Fusco N, Criscitiello C, Burstein HJ, Curigliano G. The evolving landscape of metastatic HER2-positive, hormone receptor-positive Breast Cancer. Cancer Treat Rev 2024; 128: 102761.
8. Essadi I, Benbrahim Z, Kaakoua M, Reverdy T, Corbaux P, Freyer G. HER2-Positive Metastatic Breast Cancer: Available Treatments and Current Developments. Cancers (Basel) 2023; 15: 1738.
9. Suppan C, Balic M. Current Standards and Future Outlooks in Metastatic HER2-Positive Breast Cancer. Breast Care (Basel) 2023; 18: 17-24.
10. Agostinetto E, Curigliano G, Piccart M. Emerging treatments in HER2-positive advanced breast cancer. ESMO Open 2024; 5: 101575.
11. Gampenrieder SP, Rinnerthaler G, Greil R. Treatment Landscape for Patients with HER2-Positive Metastatic Breast Cancer: New Paradigms and Emerging Treatments. Cancers (Basel) 2020; 12: 3371.
12. Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging Targeted Therapies for HER2-Positive Breast Cancer. Cancers (Basel) 2023; 15: 1987.
13. Exman P, Tolaney SM. HER2-positive metastatic breast cancer: a comprehensive review including novel agents and management of brain metastases. Clin Cancer Res 2021; 27: 4688-4698.
14. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, Ciruelos E, Schneeweiss A, Loi S, Monturus E, Clark E, Knott A, Restuccia E, Benyunes MC, Cortés J. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020; 21: 519-530.
15. Yamashita T, Saji S, Takano T, Naito Y, Tsuneizumi M, Yoshimura A, Takahashi M, Tsurutani J, Iwatani T, Kitada M, Tada H, Mori N, Higuchi T, Iwasa T, Araki K, Koizumi K, Hasegawa H, Uchida Y, Morita S, Masuda N. Trastuzumab-Pertuzumab Plus Eribulin or Taxane as First-Line Chemotherapy for Human Epidermal Growth Factor 2-Positive Locally Advanced/Metastatic Breast Cancer: The Randomized Noninferiority Phase III EMERALD Trial. J Clin Oncol 2025; 43: 1302-1313.

16. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2021; 21: 111.
17. Damuzzo V, Agnoletto L, Leonardi L, Chiumente M, Mengato D, Messori A. Analysis of Survival Curves: Statistical Methods Accounting for the Presence of Long-Term Survivors. Front Oncol 2019; 9: 453.
18. Messori A. Reconstruction of individual-patient data from the analysis of Kaplan-Meier curves: this method is widely used in oncology and cardiology – List of 173 studies in oncology and 106 in cardiology (preprint). Available at: https://osf.io/g3eyt/files/g5bfr. [Accessed on March 12, 2026]
19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: Elaboration and Explanation. BMJ 2015; 350: g7647.
20. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression Model. Biometrika 1982; 69: 239-241.