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Defining Baseline Recurrence Risk in Hormone Receptor– Positive/Human Epidermal Growth Factor Receptor–Negative Early Breast Cancer: A Meta-Analysis of Endocrine Therapy Arms From Phase 3 Trials, Including the CDK4/6 Inhibitor Era

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Defining Baseline Recurrence Risk in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor–Negative Early Breast Cancer: A Meta-Analysis of Endocrine Therapy Arms From Phase 3 Trials, Including the CDK4/6 Inhibitor Era

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Abstract

Purpose

Patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2−) early breast cancer (EBC) are at risk of invasive recurrence despite standard endocrine therapy (ET). Prior meta-analyses largely reflect historical, lower-risk populations and may not capture recurrence patterns in contemporary, high-risk cohorts. This systematic literature review and meta-analysis evaluated risk of recurrence or death (ROR) with adjuvant ET ± chemotherapy across phase 3 randomized controlled trials (RCTs) from the past 2 decades, including recent cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) trials enrolling high-risk populations.

Methods

The search identified 19 phase 3 RCTs (2003-2024) reporting invasive disease-free survival/disease-free survival in patients with HR+/HER2− EBC treated with ET ± chemotherapy. Pooled recurrence proportions at 3, 4, 5, 7, and 12 years were estimated using random-effects meta-analysis of proportions. Kaplan-Meier digitization analysis and meta-analysis among tumor characteristics and trial date subgroups were conducted.

Results

Nineteen RCTs (34 publications; >47,000 patients) met inclusion criteria. Among stage I-III patients receiving ET ± chemotherapy, pooled invasive ROR was 13% at 5 years and 27% at 12 years. At 4 years, ROR was 18% in stage II/III, 15% in node-positive, 11% in high-risk node-negative, and 7% in all-node-negative patients. Reconstructed survival curves showed a relatively constant hazard rate of ≈2%-3% per year through 12 years.

Conclusions

Phase 3 trials spanning aromatase inhibitor to CDK4/6i eras demonstrated substantial invasive ROR that emerged early and persisted through 12 years despite ET ± chemotherapy, underscoring the need for improved risk stratification and therapeutic strategy optimization beyond standard ET.

Key words: Early breast cancer; endocrine therapy; iDFS; meta-analysis; recurrence; hormone receptor positive

INTRODUCTION

Approximately 2.3 million new breast cancer cases were diagnosed globally in 2022, with projections indicating an increase to nearly 3.2 million cases by 2050 [1, 2]. Hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)-negative disease represents the most common breast cancer subtype, accounting for ≈65% of cases among women aged <50 years and 75% among those ≥50 years [3].

Standard management of HR+/HER2− early breast cancer (EBC) includes surgery followed by adjuvant endocrine therapy (ET), with or without (neo)adjuvant chemotherapy (CT) and/or radiation. ET, primarily aromatase inhibitors (AIs; anastrozole, exemestane, and letrozole) or tamoxifen, has long served as the therapy backbone[3-6]. In premenopausal patients with high-risk disease, ovarian function suppression (OFS) is often combined with ET [7, 8]. More recently, treatment options have expanded to include adjuvant cyclin-dependent kinase 4/6 inhibitors (CDK4/6is; ribociclib and abemaciclib) with ET, reflecting a shift toward treatment intensification for patients with high-risk disease. This combination provides dual targeting of endocrine signaling and key cell cycle regulators, which reduces the risk of recurrence or death (ROR) and ET resistance [9-11].

Despite these therapeutic advances prior to the availability of CDK4/6i therapies, patients with HR+/HER2− EBC remain at ROR following adjuvant therapy that varies substantially based on clinical, pathological, and genomic factors. Differences in trial populations, evolving standards of care, and variability in follow-up limit direct comparisons across studies and complicate interpretation of ROR in contemporary practice. Uncertainty regarding ROR contributes to psychological distress, especially when recurrence is unexpected [12, 13]. Many patients experiencing late recurrence may feel unprepared because they were unaware that ROR can persist for years after initial diagnosis; this is particularly relevant for patients with HR+/HER2− breast cancer [14].

A 2024 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) estimated ROR using trials conducted between 1990-2009, leaving a gap in understanding outcomes in more recent study populations [15]. Treatment paradigms have evolved over the past decade, with increased use of AIs in postmenopausal patients, OFS in premenopausal patients, and greater adoption and optimization of (neo)adjuvant CT strategies [16]. Updated estimates of ROR associated with ET in contemporary trials are therefore needed to establish a baseline for interpreting residual risk and potential benefit of treatment intensification.

Recent trials, including those evaluating CDK4/6is, have enrolled high-risk populations; however, outcomes among these patients have not been systematically manufactured [10, 11]. To address this gap, we conducted a systematic literature review (SLR) and meta-analysis of phase 3 RCTs to evaluate ROR with adjuvant ET±CT in patients with HR+/HER2− EBC, including trials that enrolled patients with high-risk disease.

Methods

SLR search

This SLR followed the Centre for Reviews and Dissemination guidelines for conducting reviews in healthcare [17]. A systematic search was conducted in Ovid on March 31, 2025, of MEDLINE,

MEDLINE In-Progress, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (**Suppl Table 1**). Several conferences were searched via Ovid or hand searched for abstracts from the previous 3 years, including the American Society of Clinical Oncology, the European Society for Medical Oncology (ESMO), ESMO Breast Cancer, and the San Antonio Breast Cancer Symposium. A supplementary hand search was completed via Google and PubMed.

SLR screening

Studies were screened independently by 2 researchers, with disagreements adjudicated by a third reviewer. Screening was conducted at 2 levels: title/abstract and then full text for studies that passed title/abstract screening. Screening decisions were guided by Population, Intervention, Comparison, Outcome, Study Design criteria (**Suppl Table 2**). Searches covered English-language phase 3 RCTs published from 2003-2024 assessing adjuvant ET use in EBC. Patient populations were required to include HR+/HER2− EBC, with adjuvant ET defined as ≥2 years of AI (anastrozole, letrozole, exemestane) and/or tamoxifen ± CT or OFS. The main outcome of interest was invasive disease–free survival (iDFS) or disease-free survival (DFS). For 12-year iDFS/DFS analysis, studies containing ≤20% HER2+ patients were permitted. Study exclusion reasons are shown in a PRISMA diagram (**Figure 1**). Publications reporting results from the same RCT were grouped.

SLR data extraction

The main outcome of interest was iDFS, typically defined as invasive ipsilateral breast tumor recurrence, local/regional recurrence, distant recurrence, death (from breast cancer, non–breast cancer, or unknown cause), invasive contralateral breast cancer, or second primary invasive cancer (non-breast cancer) [18]. DFS was used when iDFS was unavailable. The definition of DFS was not uniform across studies. DFS endpoints were accepted if they included invasive recurrence components and were deemed to approximate Standardized Definitions for Efficacy End Points–defined iDFS [18]. Data were extracted by one reviewer and audited by a second. When not reported in the text, survival data points were extracted from published Kaplan–Meier (KM) curves. Other data extracted included ET drug (letrozole, anastrozole, exemestane, tamoxifen), dosage, and duration; sample size; country; age; nodal status; tumor stage; menopausal status; ROR score; and other adjuvant treatments (including CT and concomitant OFS).

Meta-analysis feasibility

Study population, study design, sample size, and outcome availability and time points were assessed to determine feasible trials for meta-analysis at key time points. This assessment informed the methodology for meta-analysis of recurrence rates associated with adjuvant ET in the included studies. The feasibility assessment considered potential stratification by key prognostic factors: nodal status, stage, tumor size, genomic risk, trial start date, and whether the ET arm was part of a CDK4/6i trial.

Meta-analysis

ROR proportions were calculated as 1 − iDFS/DFS at 3-, 4-, 5-, and 7-year landmarks for patients with stage I–III HR+/HER2− EBC, irrespective of other prognostic factors. For studies reporting long-term follow-up, 12-year iDFS/DFS and overall survival estimates were extracted.

Pooled estimates were generated using a meta-analysis of proportions with inverse-variance weighting and Freeman–Tukey double-arcsine transformation. A random-effects model was applied to account for interstudy heterogeneity. Analyses were conducted in R using the meta package, and heterogeneity was quantified using the I^2 statistic. Sensitivity analyses restricted to studies including all nodal categories (N0-N3) were performed.

To further address heterogeneity, prespecified subgroup analyses were conducted at the 4-year time point (longest duration with sufficient subgroup data), including all node-negative (N0), high-risk node-negative (N0 with genomic high risk; e.g., Oncotype DX® Recurrence Score ≥26, MammaPrint high-risk, tumor grade 3, or stage II/III disease), or any high-risk population (per trial-specific eligibility criteria and including N0 high-risk disease and/or N+ disease meeting trial-specific high-risk criteria, with high-risk features such as high genomic or clinicogenomic risk, anatomic stage II/III disease, grade 3 disease, elevated Ki-67, larger tumor size, residual disease after neoadjuvant CT, and/or high nodal burden) and control arms of CDK4/6i trials.

KM digitization

In an exploratory analysis, KM curves from eligible ET arms were digitized to reconstruct individualized patient-level time-to-event data and generate aggregated survival curves. KM coordinates were extracted [19], and event times were reconstructed using the Guyot algorithm [20]. Digitized coordinates were aligned with reported numbers at risk at each time point and, where available, total event counts. Reconstructed datasets were combined to create aggregated patient-level datasets, and survival estimates were derived using the survfit function in the survival package in R [21]. Hazard rates were estimated by converting KM survival functions to cumulative hazards and applying kernel smoothing techniques. A 4-year survival curve was constructed from trials with ≥4 years of follow-up and a 12-year curve from trials with ≥12 years of follow-up, representing the duration available for meaningful aggregation. Smoothed annualized rates of recurrence during the first 4 and 12 years were estimated from reconstructed pooled KM curves using the muhaz package in R with an Epanechnikov kernel and local bandwidth smoothing. Due to incomplete reporting of numbers at risk and limited information on censoring, censoring was assumed to be non-informative.

Results

Screening results

The OVID search identified 1,832 papers, with 5 additional papers identified through manual searching. Nineteen trials, reported across 34 papers, met the eligibility criteria (**Figure 1**) [7, 10, 22-54].

Publications

Seven trials were based in 6 countries (US, Germany, Italy, Japan, Spain, South Korea); the remaining 12 were international (**Suppl Table 3**). Five trials had a physician's-choice arm of AI (anastrozole, letrozole, or exemestane) or tamoxifen. Daily doses for ET were letrozole 2.5 mg, anastrozole 1 mg, tamoxifen 20 mg, or exemestane 25 mg. Sample size ranged from 354 in HOBOE [27] to 4,690 (overall population) in SOFT/TEXT [7]. Median age ranged from 40 years in ASTRRA [50, 54] to 62 years in FACE [25] and GEICAM [26].

Based on feasibility, among trials with a clear survival curve or reported rate, 15, 15, 15, and 6 were eligible for 3-, 4-, 5-, and 7-year iDFS/DFS rates, respectively (**Table 1**). Because few trials reported 10-year iDFS/DFS rates (n=2), a 10-year meta-analysis was not feasible. For 12-year iDFS/DFS analysis, studies with ≤20% HER2+ patients were permitted. Five studies with HER2+ patient populations (0%-14.2%) were included. A separate sensitivity analysis included 9 trials with all nodal status categories (N0-N3), removing trials that only included N0 or only N1.

There were ≥3 trials with 4-year data for the following subgroups: all N0, N0 high-risk (N0 and genomic high risk; e.g., Oncotype DX® Recurrence Score ≥26, MammaPrint high-risk, or tumor grade 3 or stage II/III disease per the American Joint Committee on Cancer), N+, and any high-risk disease (per trial-specific eligibility criteria, including N0 high-risk and/or N+ disease meeting trial-specific high-risk criteria, with high-risk features such as high genomic or clinicogenomic risk, anatomic stage II/III disease, grade 3 disease, elevated Ki-67, larger tumor size, residual disease after neoadjuvant CT, and/or high nodal burden); stage I or <30% tumor size <2 cm (T1); stage II/III only; control arms of CDK4/6i studies; and trial start date (1998-2009 or 2010-2019) (**Table 1**).

Overall results

Data were extracted, including >47,000 patients (stage I-IIIC). The 4-year pooled ROR across patients with stage I-IIIC HR+/HER2− disease on ET±CT was 10% based on all eligible trials, irrespective of the nodal populations enrolled (15 trials; n=34,711), and 13% in the sensitivity analysis restricted to trials that enrolled patients in every nodal category (N0-N3; 9 trials; n=13,189) (**Tables 1 and 2; Figure 2; Suppl Figure 7**).

Subgroup results

The 4-year pooled RORs across ET±CT arms were 7% (6 trials; n=12,055) for all N0 patients and 15% for N+ (6 trials; n=7,583) (**Table 2; Suppl Figures 8 and 9**). In the N0 high-risk subgroup, the 4-year pooled ROR was 11% (5 trials; n=2,121) (**Table 2; Suppl Figure 10**). For trials including all patients with high-risk disease, the 4-year pooled ROR was 17% (10 trials; n=12,756) (**Table 2; Suppl Figure 11**). In trial arms in which <30% of patients had stage I or T1 disease, the 4-year pooled ROR was 18% (6 trials; n=10,491) (**Table 2; Suppl Figure 12**). For trials with only stage II/III disease, the 4-year pooled ROR was 18% (3 trials; n=6,094) (**Table 2; Suppl Figure 13**). The 4-year pooled ROR across ET±CT arms included as control arms in the 4 CDK4/6i trials (n=8,877) was 20% (**Table 2; Suppl Figure 6**). The 4-year pooled ROR was 7% (n=15,371) in the 6 trials with start dates between 1998 and 2009 and 13% (n=19,340) in the 9 trials with start dates between 2010 and 2019 (**Table 2; Suppl Figures 14 and 15**).

Overall survival

The 12-year pooled ROR across patients with stage I-IIIC disease receiving ET±CT, regardless of nodal status (5 trials; n=20,668), was 27%, and pooled overall survival was 88% (**Table 2; Suppl Figures 4 and 5**).

KM digitization

Five trials had ≥12 years of follow-up and extractable KM plots (n=11,545 with stage I-III EBC), regardless of nodal status (**Figure 5**). Among these patients, 2,776 events were observed. The estimated 12-year iDFS/DFS rate was 71.5%, corresponding to an ROR of ≈28.5%, consistent with the pooled 12-

year meta-analysis estimate of 27%. The curve demonstrated a declining survival trajectory without evidence of a plateau. For the 4-year aggregated KM curve (15 trials), the total sample was 34,711 patients and 3,202 events were observed (**Figure 4**). The estimated 4-year iDFS/DFS rate was 89.7%, corresponding to an ROR of 10.3%, in line with the 10% pooled recurrence rate identified in the meta-analysis. A 4-year aggregated KM curve was generated for trials reporting outcomes across all N0-N3 subgroups (**Suppl Figure 16**): Among 6,265 patients, 1,600 events were observed, with an estimated 4-year iDFS/DFS rate of 86.1% (ROR ≈13.9%). This estimate was consistent with the pooled 13% recurrence rate for N0-N3 disease in the meta-analysis.

Hazard-rate functions derived from the aggregated KM curves indicated a relatively stable recurrence hazard (range, 2%-3% per year), continuing across time periods (0-5 and >5 years) (**Figure 3; Suppl Figures 17**).

Discussion

This meta-analysis in patients with stage I-III HR+/HER2− EBC from trials published between 2003 and 2024 demonstrates that risk of invasive recurrence emerges early during adjuvant therapy and persists beyond 5 years despite standard ET±CT, with cumulative incidence increasing from 7% at 3 years to >13% at 5 years. Given the inclusion of stage I disease, irrespective of nodal status, these estimates may be conservative; consistent with this, subgroup analyses showed higher ROR when lower-risk patients were excluded. When patients with stage I or T1 tumors comprised <30% of the population or analyses were restricted to stage II/III disease, recurrence reached ≈18% by 4 years. These findings suggest that overall EBC recurrence estimates are largely driven by patients with stage II/III disease.

Risk of late (>5 years) recurrence for stage I-III EBC remained high, rising to 15% at 7 years and up to 27% at 12 years. These findings highlight a need to reduce late recurrences, which can be driven by acquired resistance to ET or activation of dormant micrometastatic disease, in addition to early recurrences, which are often driven by intrinsic endocrine resistance[55-58].

Approximately 44% of patients across the 19 trials had N0 disease with heterogeneous risk profiles. The 4-year ROR was 7% in all patients with stage I-III N0 disease but increased to 11% in those with additional high-risk features, including larger tumor size, high grade, or elevated genomic risk. These findings underscore heterogeneity within the N0 population and the need to identify patients with clinically meaningful ROR despite standard ET.

When stratified by trial initiation period, the 4-year ROR was 6% higher in trials initiated between 2010 and 2019 vs those initiated between 1998-2009 (13% vs 7%, respectively). This likely reflects differences in trial populations over time. More recent studies, including those evaluating targeted therapies such as CDK4/6i, have preferentially enrolled patients with high-risk stage II/III disease, thereby identifying patients with high baseline ROR who may likely benefit from CDK4/6i therapy .

The reconstructed KM curves corroborated the meta-analysis findings. The reconstructed 4- and 12-year survival estimates illustrate the temporal risk pattern, while hazard-rate analyses suggest a relatively constant recurrence rate, ≈2%-3% per year. Although these findings reflect aggregate trends and hazard patterns may differ across specific clinical or biological subgroups, limited availability of long-term

subgroup follow-up data precluded detailed exploration of KM trajectories within these subgroups. Importantly, evidence of ROR attenuation over time was found; persistent, ongoing, long-term risk was observed throughout follow-up.

To our knowledge, this is the first SLR and meta-analysis to assess ET arms of CDK4/6i trials. Our findings should be interpreted in the context of the recent EBCTCG meta-analysis [59], which reported a decline in ROR over time in patients enrolled between 1990-1999 and 2000-2009. These differences are attributable to methodological and population-level distinctions. The EBCTCG study applied additional eligibility restrictions, excluding patients with tumors >50 mm or ≥10 positive nodes or older patients (≥75 years), thereby focusing on a more selective, lower-risk population. In contrast, our meta-analysis did not impose such exclusions and reflects broader populations enrolled in contemporary trials. The EBCTCG analysis was restricted to trials conducted up to 2009, whereas our study captures more recent evidence, including trials of targeted therapies (e.g., CDK4/6is) that have preferentially enrolled high-risk stage II/III populations. Another distinction relates to outcome definitions. The EBCTCG analysis focused specifically on distant recurrence, whereas our meta-analysis evaluated invasive recurrence events overall, encompassing distant and locoregional recurrences as well as new invasive primaries and deaths [59]. Differences in endpoint definitions and underlying patient risk profiles may contribute to the higher recurrence estimates observed in our analysis relative to EBCTCG. Higher recurrence rates in more recent trials likely reflect differences in patient selection and outcome definitions as well as earlier detection methods/improved screening rather than reversal of therapeutic progress. Indeed, the EBCTCG investigators demonstrated that much of the observed temporal improvement was driven by shifts toward lower-risk populations and earlier-stage disease, alongside advances in treatment [59]. These analyses should be viewed as complementary rather than conflicting: The EBCTCG study highlights improvements in distant recurrence under historical, more selective trial conditions, whereas our findings provide contemporary perspective on residual invasive ROR in broader, high-risk populations that are more reflective of current therapeutic development and decision-making contexts. Both analyses demonstrate substantial long-term risk in patients with HR+/HER2− EBC (i.e., substantial risk of late recurrence).

The subgroup analyses highlight the clinical relevance of early ROR in populations, most reflective of current therapeutic development. The overall 4-year risk of invasive recurrence among all stage I-III N0 patients was 7% but increased to 11% in those with additional high-risk features (high genomic risk, greater tumor size, or higher grade), underscoring clinically meaningful heterogeneity within N0 disease. This heterogeneity is important for patients to consider in shared-decision making with physicians given their individual risk of recurrence and perceived benefit from adjuvant therapies, such as CDK4/6is. Four-year risk was substantially higher in more risk-enriched populations, reaching 18% in stage II/III disease and 20% in the control arms of CDK4/6i trials, indicating that a considerable proportion of events occur within the first few years of adjuvant ET in these groups. Early event rates in risk-enriched subgroups may represent only the initial portion of a risk trajectory that extends beyond our analysis. Although direct extrapolation is limited by differences in populations and endpoints, the persistent long-term hazard observed by EBCTCG raises the possibility that patients with high-risk features, such as those in stage II/III cohorts and CDK4/6i trial populations, may continue to experience clinically meaningful ROR over extended follow-up [59]. These observations emphasize that early recurrence is a significant component of overall disease burden in high-risk populations and underscore the need for longer-term follow-up in contemporary, risk-enriched cohorts to fully characterize the trajectory of ROR and inform strategies for

sustained disease control. Recent real-world evidence demonstrating persistent recurrence risk through 10 years and beyond among patients with stage II-III HR+/HER2− EBC with N1 disease further highlights long-term ROR increases over time; similar studies for other high-risk populations are warranted.[60]

A key strength of our study is the application of 2 complementary analytic approaches, in which reconstructed KM curves provided visual information and useful cross-validation of landmark meta-analysis results. Several assumptions and limitations should be considered when interpreting these findings, including interstudy heterogeneity. Meaningful differences in patient populations, trial designs, and outcome definitions across studies cannot be fully eliminated. A random-effects meta-analysis assumes that included trials represent a random sample of a broader set of studies, and that between-study variability occurs at random; however, residual heterogeneity may still influence pooled estimates. An additional limitation is that this meta-analysis is based on aggregate trial-level data rather than individual patient data, which is considered the gold standard for meta-analyses.[17] As a result, harmonization of outcome definitions, adjustment for patient-level covariates, and more granular subgroup or multivariable analyses were limited; however, the large sample size, inclusion of contemporary trials, and consistency of findings across analyses support the overall robustness of the results.

Subgroup analyses were conducted to partially address heterogeneity and explore the impact of key clinical variables; however, these analyses inherently reduce the available sample size and have limited ability to evaluate multiple interacting factors simultaneously. Additionally, subgroup definitions and reporting were not uniform across studies, and results in specific subgroups were not consistently available. Long-term follow-up data were also limited. Several studies did not report outcomes beyond 5 years, and, at the time of this analysis, no CDK4/6i trials have reported 7-year iDFS/DFS outcomes. These gaps restrict the ability to fully characterize long-term recurrence trajectories, particularly within contemporary, high-risk clinical trial populations. Future research is needed to validate and extend these findings. As more trials mature and report long-term and subgroup-specific outcomes, incorporation of these data into meta-regression models may enable a more refined understanding of the multiple factors influencing ROR over time.

Conclusions

In summary, this meta-analysis provides a contemporary assessment of ROR in HR+/HER2− EBC across the transition to the CDK4/6i era. The findings indicate that invasive recurrence both emerges early during the adjuvant period and persists over time, with particularly elevated risk observed in clinically risk-enriched populations, including high-risk N0 and stage II/III disease. By establishing a modern baseline of ROR associated with ET monotherapy across diverse and risk-stratified populations, this analysis offers important context for interpreting the clinical benefit of treatment intensification strategies. These data underscore the need for identifying patients at risk and more effective therapeutic approaches beyond single agent ET to address the continuum of recurrence, both early and late, in HR+/HER2− EBC.

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Statements & Declarations

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Competing Interests

E Hamilton reports grants from Novartis during the conduct of the study. Outside the submitted work, she reports grants from Hutchinson MediPharma, OncoMed, MedImmune, Stem CentRx, Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Millennium, TapImmune, BerGenBio, Kadmon, H3 Biomedicine, Radius Health, Acerta Pharma, Takeda, MacroGenics, AbbVie, Immunomedics, Fujifilm, eFFECTOR Therapeutics, Mallinckrodt, Merus, Nucana, TetraLogic Pharmaceuticals, PharmaMar, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, Syros, CytomX, InventisBio, and Oncothyreon; nonfinancial support from Amgen, Bayer, Bristol Myers Squibb, Genzyme, Helsinn Therapeutics, HERON, Lexicon, Merck, Sysmex, Guardant Health, and Foundation Medicine; personal fees from Flatiron; grants and other from Pfizer, Puma Biotechnology, Mersana, Boehringer Ingelheim, and Cascadian Therapeutics; grants and nonfinancial support from AstraZeneca, Tesaro, EMD Serono, Clovis, Medivation, and Novartis; and grants, nonfinancial support, and other from Genentech/Roche, Lilly, Daiichi Sankyo, and Eisai. **K Kalinsky** reports employment stock of spouse from EQRX, Grail (prior employee); personal fees for advisory/consulting from Eli Lilly, Pfizer, Novartis, AstraZeneca, Daiichi Sankyo, Puma, 4D Pharma, Oncosec, Immunomedics, Merck, Seattle Genetics, Mersana, and Cyclocel; and institutional research funding from Genentech/Roche, Novartis, Lilly, AstraZeneca, Daiichi Sankyo, and Ascentages. **P Tarantino** reports advisory boards, speaker fees, and consulting fees from AstraZeneca, Daiichi Sankyo, Novartis, Gilead, Eli Lilly, and Roche. **N McAndrew** reports other from Novartis, during the conduct of the study; personal fees from Novartis, outside the submitted work; additional contracted research funding paid to his institution from Novartis, Daiichi Sankyo, Seattle Genetics, and Dizal; advisory board honorarium from Daiichi Sankyo, Biotheranostics, and Genomic Health; consulting honorarium from Daiichi Sankyo, AZ, and GoodRx; and travel accommodation from Translational Research in Oncology (TRIO), Daiichi Sankyo, and Roche. **Y-Shen Lu** reports a grant for clinical study; advisory board consultation fee/speaker fee from NVS; consultation fee from Pfizer; contracted research, speaker fee from Roche; grants, contracted research, and speaker fees from Merck Sharp & Dohme, Pfizer, and AZ; speaker fees from Eisai and Eli Lilly; speaker fees and advisory board fees from Daichii Sankyo. **P A Fasching** reports personal fees for advisory boards from Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, Eisai, Merck Sharp & Dohme, Eli Lilly, Pierre Fabre, Seagen, Roche, Hexal, Agendia, Sanofi Aventis, Gilead; institutional funding grant from BioNtech, Cepheid; research grant from Pfizer. **E M Ciruelos** reports personal fees from Roche, Lilly, Novartis, and Pfizer, during the conduct of the study. **V Ganapathy, C Auld** report employment from Novartis. **D Proudman, A Kwok, O Shane, D Nellesen** report employment for Analysis Group, Inc., a consulting company which received funding from Novartis for this study. **G Curigliano** reports consulting fees from BMS, Roche, Pfizer, Novartis, Lilly, AstraZeneca, Daiichi Sankyo, Merck, Seagen, Ellipsis, Gilead, and Menarini; personal fees from Lilly, Pfizer, Relay, Gilead, Novartis, and Menarini; and travel support from Daichii Sankyo

Author Contributions

All authors contributed to the study conception, study design, and interpretation of the data. Material preparation, data collection, and analysis were performed by Adrienne Kwok, Dave Nellesen, David Proudman, and Olivia Shane. The manuscript was drafted and critically revised by all authors, who read and approved the final manuscript.

Data Availability

All data analyzed in this study were obtained from publicly available published clinical trials. Extracted datasets, reconstructed survival data, meta-analysis code, and all supplementary materials are available from the corresponding author upon reasonable request.

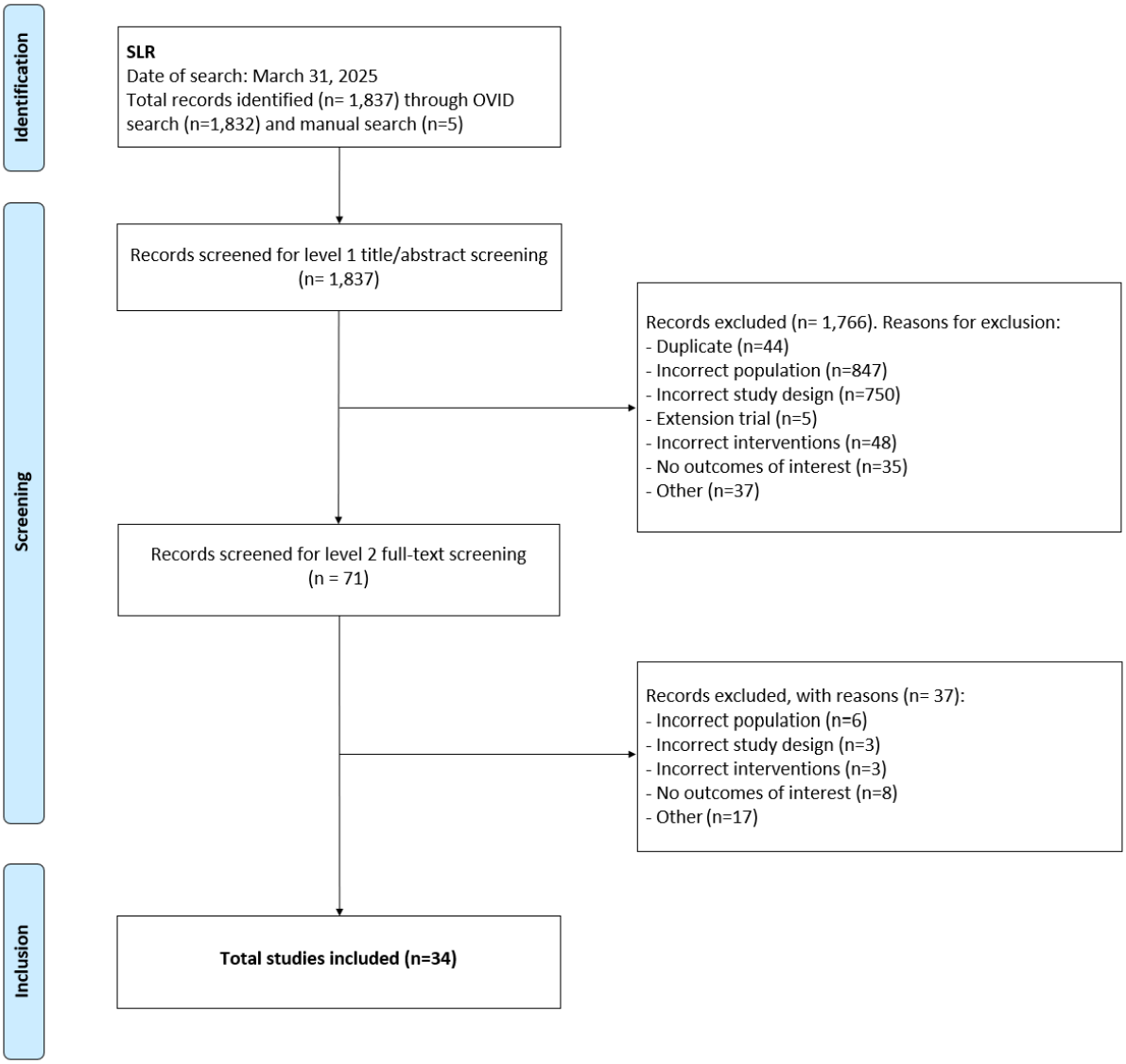
Human Ethics and Consent to Participate declarations: not applicable

Ethics Approval

Institutional Review Board approval was not required for this systematic literature review and meta-analysis because the study used aggregate data from previously published clinical trials and did not involve the collection or analysis of individual patient-level data.

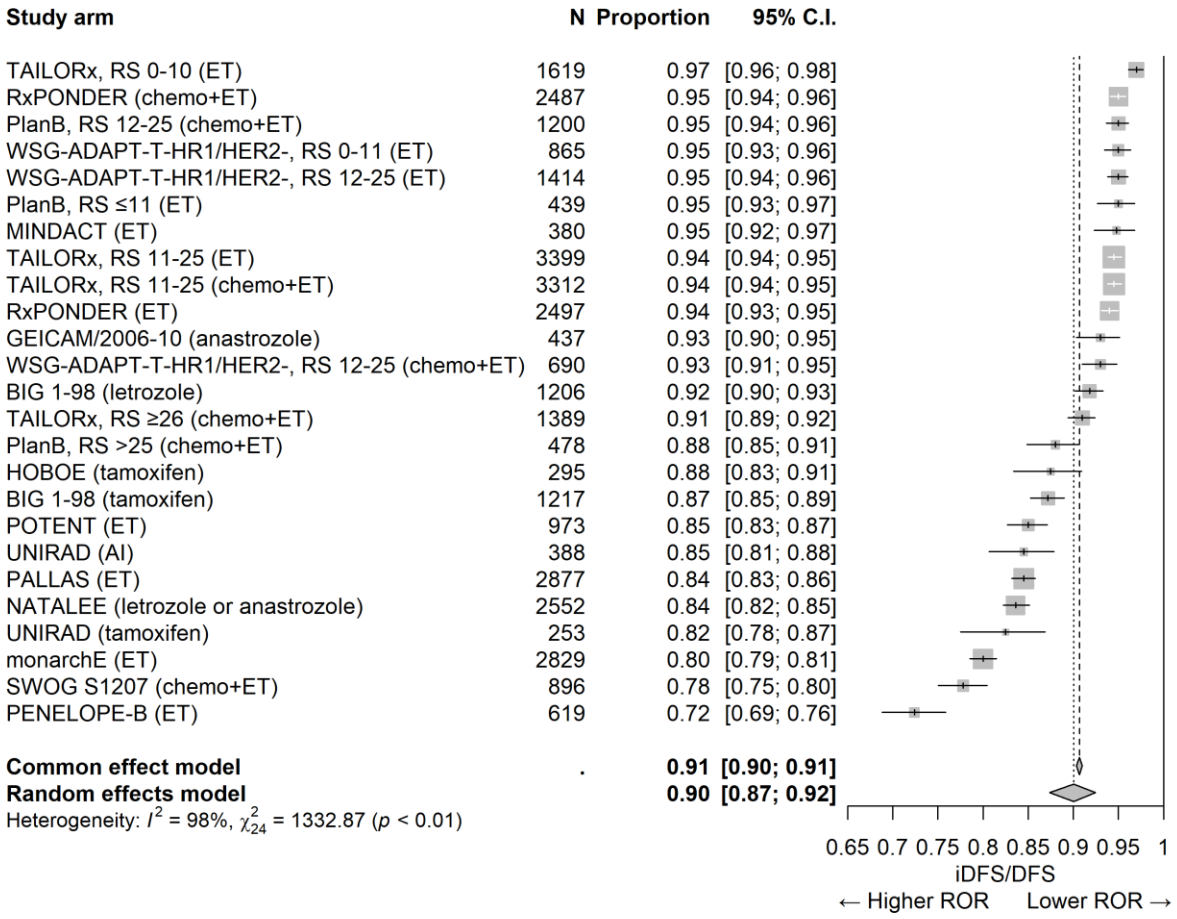
Figures and Tables

Fig. 1 PRISMA diagram



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

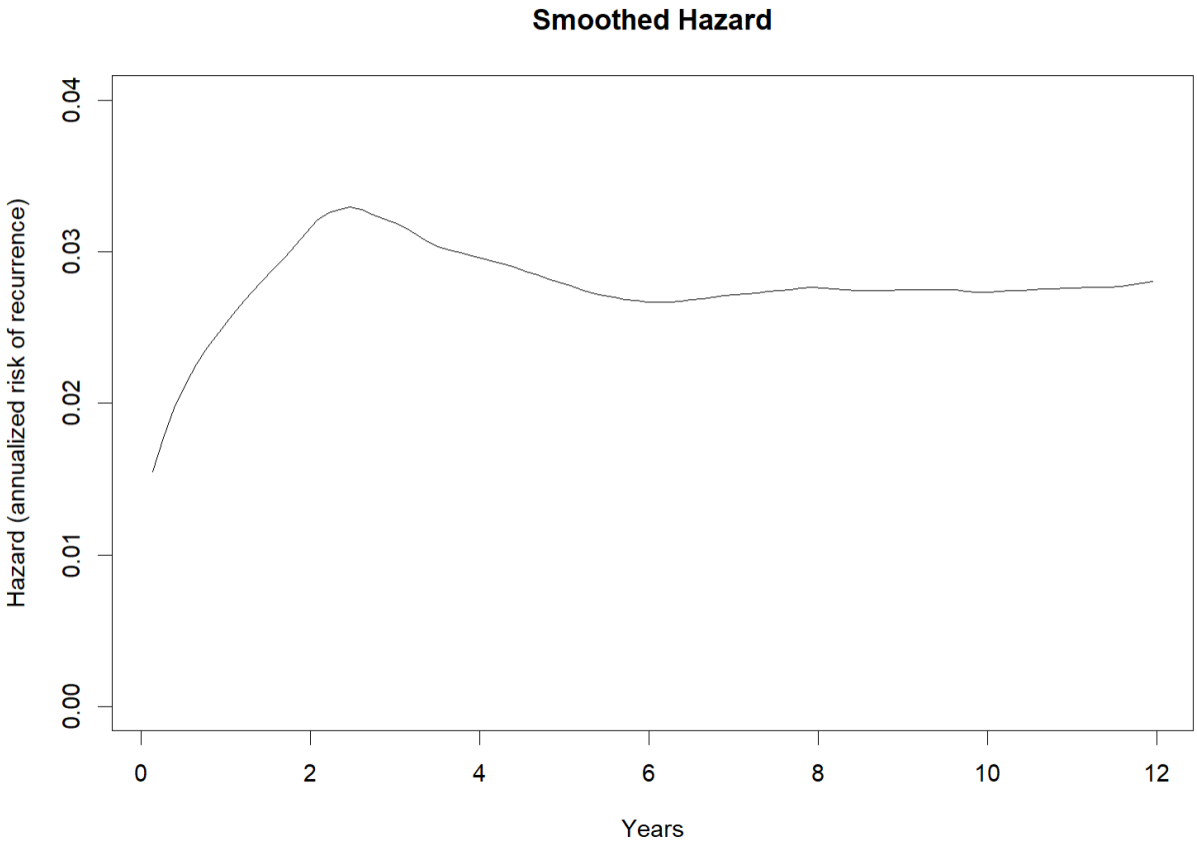
Fig. 2 Forest plot of studies reporting 4-year iDFS/DFS, regardless of nodal status[a,b]



Abbreviations: AI, aromatase inhibitor; DFS, disease-free survival; ET, endocrine therapy; iDFS, invasive disease–free survival; ROR, risk of recurrence.

[a]Includes all eligible trials that reported iDFS and/or DFS, regardless of nodal status being reported. [b]The vertical lines on the forest plot denote the pooled mean iDFS of the common-effects and random-effects model.

Fig. 3 12-year iDFS/DFS curve hazard rate over time[a]



Abbreviations: DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease–free survival.

[a]Includes populations with up to 20% HER2+.

Table 1. Overall results (ROR and OS in patients with stage I-III EBC treated with ET±CT)

		Overall results			
		No. of unique trials	**Sample size (aggregated)**	**ROR rate/OS (CI), %**	**Corresponding forest plot**
Overall ROR rate (CI), %	**3-y**	15	34,711	7 (5, 9)	Suppl Figure 1
	4-y	15	34,711	10 (8, 13)	Figure 2
	5-y	15	35,494	13 (10, 16)	Suppl Figure 2
	7-y	6	16,711	15 (11, 20)	Suppl Figure 3
	12-y	5	21,264	27 (23, 31)	Suppl Figure 4
Overall OS rate (CI), %	**12-y**	5	20,668	88 (84, 90)	Suppl Figure 5

Abbreviations: CT, chemotherapy; EBC, early breast cancer; ET, endocrine therapy; OS, overall survival; ROR, risk of recurrence.

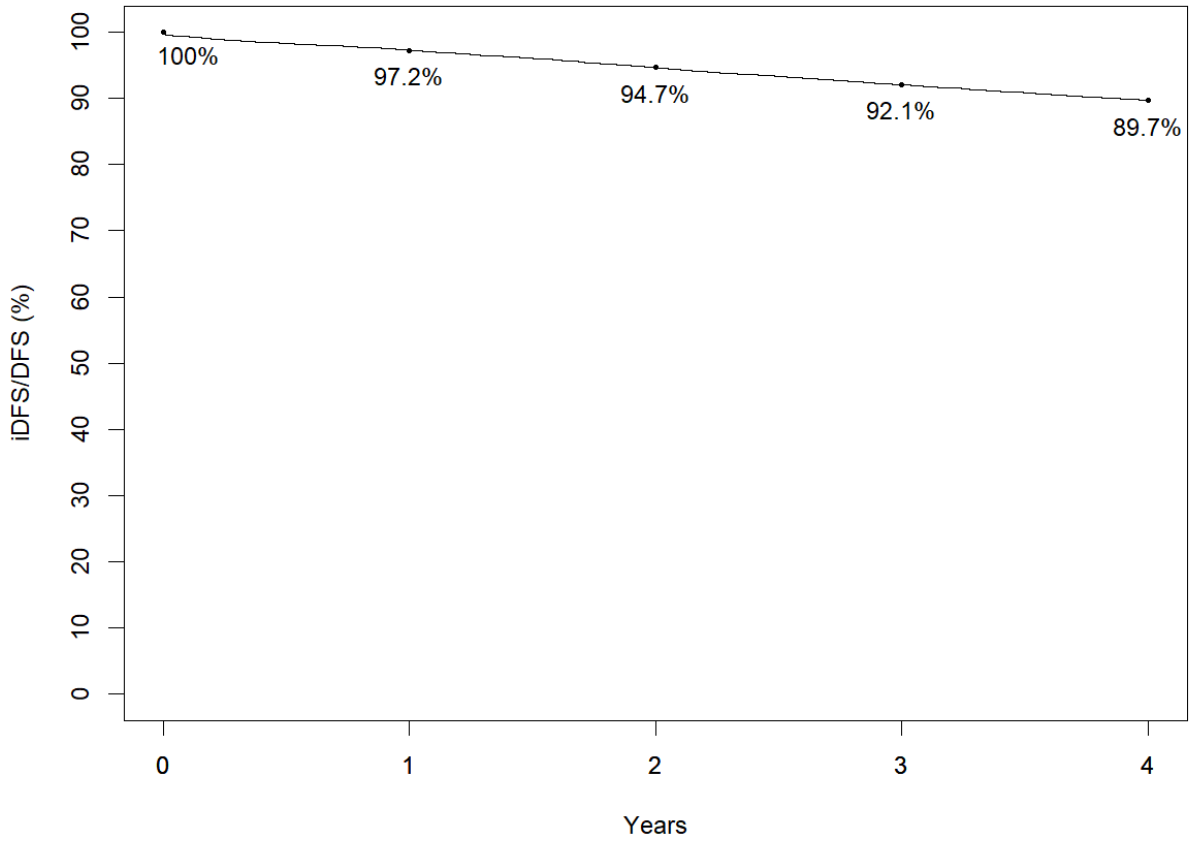
Table 2. Subgroup results at the 4-year time point (ROR in ET±CT arms with stage I-III EBC treated with ET ± CT)

	Subgroups									
	CDK4/6i trial control	**N0-N3**	**N+**	**N0**	**N0, high risk[a]**	**High risk[b]**	**<30% stage I/T1**	**Stage II/III**	**Trial start date 1998-2009**	**Trial start date 2010-2019**
No. of unique trials	4	9	6	6	5	10	6	3	6	9
Sample size (aggregated)	8,877	13,189	7,583	12,055	2,121	12,756	10,491	6,094	15,371	19,340
ROR rate (CI), %	20 (12, 29)	13 (9, 17)	15 (10, 21)	7 (4, 10)	11 (5, 18)	17 (13, 20)	18 (14, 22)	18 (13, 23)	7 (5, 9)	13 (9, 18)
Corresponding forest plot	Suppl Figure 6	Suppl Figure 7	Suppl Figure 8	Suppl Figure 9	Suppl Figure 10	Suppl Figure 11	Suppl Figure 12	Suppl Figure 13	Suppl Figure 14	Suppl Figure 15

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; EBC, early breast cancer; ET, endocrine therapy; ROR, risk of recurrence.

[a]For N0 subgroups, high risk was primarily defined using genomic risk scores (e.g., Oncotype DX® Recurrence Score ≥26, MammaPrint high risk) and, in some studies, additional clinical features (e.g., tumor grade or stage II/III disease per American Joint Committee on Cancer).
[b]High-risk populations were defined according to trial-specific eligibility criteria and included N0 high-risk disease and/or N+ disease meeting trial-specific high-risk criteria. Criteria varied by study and included high genomic or clinicogenomic risk, such as Oncotype DX Recurrence Score ≥26 or >25, MammaPrint high risk, or EndoPredict/EPclin ≥3.3; anatomic stage II/III disease; grade 3 disease; elevated Ki-67; tumor size thresholds; residual invasive disease after neoadjuvant chemotherapy; and/or nodal burden, such as ≥4 positive lymph nodes. Study-specific high-risk definitions are provided in the footnotes to Supplemental Figure 11.

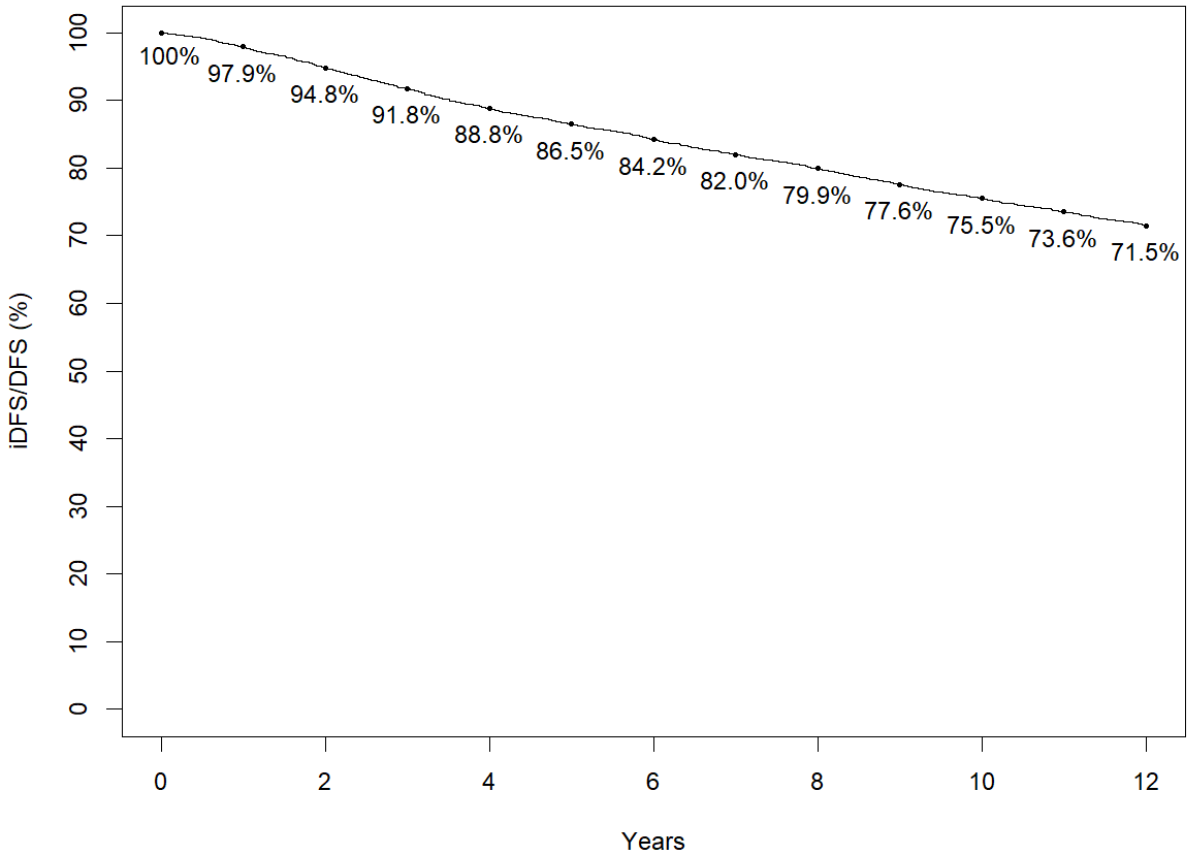
Fig. 4 Reconstructed aggregate KM curve, 4-year iDFS/DFS regardless of nodal status[a]



Abbreviations: DFS, disease-free survival; iDFS, invasive disease–free survival; KM, Kaplan–Meier.

[a]Includes all eligible trials that reported iDFS and/or DFS, regardless of lymph node status being reported.

Fig. 5 Reconstructed aggregate KM curve, 12-year iDFS/DFS, regardless of nodal status[a]



Abbreviations: DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease–free survival; KM, Kaplan–Meier.

[a]Includes all eligible trials that reported iDFS and/or DFS, regardless of lymph node status being reported, including populations with up to 20% HER2+.

Supplementary Files

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