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ORIGINAL ARTICLE

Correlation analysis of invasive disease-free survival and overall survival in a real-world population of patients with HR+/HER2– early breast cancer

Stephanie L. Graff MD, FACP, FASCO[1] | Sara M. Tolaney MD, MPH[2] | Lowell L. Hart MD, FACP[3,4] | Pedram Razavi MD, PhD[5] | Wolfgang Janni MD, PhD[6] | Lee S. Schwartzberg MD, FACP[7] | Andriy Danyliv PhD[8] | Murat Akdere PharmD[8] | Ilia Ferrusi PhD[9] | Rishi Rajat Adhikary PhD[10] | Joyce A. O'Shaughnessy MD[11]

[1]Brown University Health Cancer Institute, Legorreta Cancer Center at Brown University, Providence, Rhode Island, USA

[2]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[3]Florida Cancer Specialists, Sarah Cannon Research Institute, Fort Myers, Florida, USA

[4]Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[5]Memorial Sloan Kettering Cancer Center, New York, New York, USA

[6]Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany

[7]Renown Health-William N. Pennington Cancer Institute, Reno, Nevada, USA

[8]Novartis Pharma AG, Basel, Switzerland

[9]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

[10]Novartis Healthcare Pvt., Ltd, Hyderabad, Telangana, India

[11]Texas Oncology/Baylor University Medical Center, Dallas, Texas, USA

Correspondence
Stephanie L. Graff, 593 Eddy St, George 304, Providence, RI 02903, USA.
Email: sgraff1@brownhealth.org

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Abstract

Background: Overall survival (OS) is the gold standard for assessing clinical benefit in oncology but requires extended follow-up to detect sufficient events. Invasive disease-free survival (iDFS) requires shorter follow-up times and is considered an objective and clinically meaningful end point in early breast cancer (EBC) trials. The authors assessed iDFS as a surrogate end point for OS in adjuvant HR+/HER2– EBC using real-world patient-level data.

Methods: A retrospective analysis was conducted on patient data from the ConcertAI Patient360 database (January 1995–April 2021). Key inclusion criteria: age ≥18 years, stage II or III (AJCC 8th Edition) HR+/HER2– EBC, prior surgery, adjuvant endocrine therapy (ET). Spearman ρ, iterative multiple imputation ρ (IMI; 0.8–1 considered "very strong"), and R^2 (clinical relevance $R^2 \geq 0.70$) were used to assess iDFS–OS relationship. Subgroup analyses included ET (nonsteroidal aromatase inhibitor or tamoxifen), stage, menopausal status, nodal status, prior (neo)adjuvant chemotherapy, and prior radiotherapy.

Results: A total of 3133 patients were included (1103 [35.2%] iDFS events; 554 [17.7%] OS events); mean age was 58.4 years, 98.8% were female, 29.9% were premenopausal, and 80.9% had stage II disease. Median follow-up time was 55.1 months. iDFS and OS exhibited a positive, very strong, clinically relevant correlation (Spearman ρ: 0.88 [0.87–0.89]; IMI ρ: 0.83 [0.79–0.86]; both $p < .0001$). iDFS accounted for 82% of variation in OS ($R^2 = 0.82$). Results of all subgroup analyses were consistent with overall population.

Conclusions: This patient-level real-world analysis demonstrated very strong, positive correlations between iDFS and OS, supporting the use of iDFS as a reliable primary end point in adjuvant HR+/HER2– EBC.

KEYWORDS
correlation analysis, HR+/HER2− early breast cancer, invasive disease-free survival, overall survival, real world

INTRODUCTION

Treatment for patients with HR+/HER2 early breast cancer (EBC) is conducted with curative intent, with overall survival (OS) as the ultimate measure for treatment efficacy. Although OS is the "gold standard" end point in clinical trials, a challenge is the extended follow-up periods needed to detect sufficient events for adequately powered analysis.[1] This may limit the use of OS as the primary end point in some oncology trials.[1] This limitation is particularly relevant in breast cancer (BC), where standard-of-care targeted therapies have improved outcomes in metastatic disease, making it even more challenging to demonstrate OS benefit in EBC.[2] Without an earlier option to detect clinically meaningful improvements in outcomes, patient access to innovative adjuvant treatments would be much delayed in the clinical setting.

A strategy to overcome this delay involves using a clinically relevant surrogate end point that can be measured at an earlier time point, such as disease-free survival (DFS), as an alternative to evaluating OS.[1] In numerous oncology trials, DFS has been investigated as an alternative for OS.[3–10] In adjuvant EBC, the introduction of Standardized Definitions for Efficacy End Points (STEEP) criteria has led to the acceptance of invasive DFS (iDFS) as a clinically and patient-meaningful primary end point in clinical trials (with additional alternatives [e.g., invasive breast cancer–free survival in STEEP 2.0] depending on trial design), and iDFS has been recognized by several regulatory authorities.[1,10–13] However, validation of iDFS as a surrogate end point for OS in HR+/HER2− EBC is still needed.[14]

Analysis of data from randomized controlled trials (RCTs) is one approach used to validate surrogate end points.[15] A prior correlation analysis using data from RCTs (including trial- and patient-level data) showed that DFS/iDFS was an effective surrogate end point for OS in the adjuvant setting in patients with HR+/HER2− EBC.[12] However, one limitation of that study was the heterogeneity of iDFS/DFS definitions in RCTs, which spanned almost 2 decades. Although both DFS and iDFS were included as reported by respective RCTs, iDFS is arguably the more relevant end point due to its standardization in EBC and use in more-recent RCTs.[16–19] Additionally, there is an increasing need to understand how data in the RCT setting correlate to real-world populations, including for surrogate end points.[20] In this analysis, we used data from a real-world population of patients with HR+/HER2− EBC receiving adjuvant treatment to assess outcome-level surrogacy between iDFS and OS. The focus of this analysis was on the postoperative adjuvant stage, where DFS end points are often used in clinical trials. In our case, we chose iDFS as it has been defined by STEEP as a standardized end point in EBC trials.

MATERIALS AND METHODS

Overview

This was a noninterventional, retrospective cohort study of patients enrolled in the ConcertAI Patient360 breast cancer database (data cutoff dates: January 1, 1995, to April 30, 2021). The ConcertAI database includes deidentified electronic medical records of a cohort of 6 million patients treated at 400+ US academic (30%) and community (70%) oncology clinics.

Study population

Patients in the ConcertAI Patient360 database with a curated diagnosis of BC were eligible for inclusion in the analysis ("BC cohort"). Additional eligibility criteria included nonmissing sex and age 18 years and older at initial diagnosis, HR+ (estrogen or progesterone receptor positive)/HER2−, anatomic stage II or III (AJCC 8 [American Joint Committee on Cancer's *Cancer Staging Manual*, 8th edition]) disease with a residual tumor status of 0. Staging was based on the earliest curated stage from the date of diagnosis (in the absence of curated entry, the worst pathological staging information was prioritized). Patients were required to have undergone relevant surgery and treatment with at least one qualifying adjuvant endocrine therapy (ET) regimen (tamoxifen or nonsteroidal aromatase inhibitor [NSAI; anastrozole or letrozole]; ovarian function suppression was permitted). In the time period before first qualifying surgery, patients were required to have an ER-positive or PR-positive and HER2-negative result for their disease; patients with missing data with respect to major variables like surgery and HR/HER2 status were not included. Patients were required to have an index date (first ET initiation post resection surgery) of 6 months or more before the data cutoff date of April 30, 2021. Before the index, the patients should have no assessment date for recurrent tumors and no record of other concurrent invasive malignancy. Patients meeting all the inclusion criteria ("EBC cohort") were included in the analysis.

Statistical analyses

iDFS (per STEEP and incorporating the events of disease recurrence, metastasis, second primary tumor, or death) and OS (reflecting death due to any cause) were defined as the time between the start of ET and the first qualifying event. Patients who did not experience an event were censored at the time of data cutoff or maximum follow-up

(whichever occurred first) for iDFS and at maximum follow-up for OS.[21] Disease recurrence was identified through observation of a "tumor progression" ("Recurrent tumor" in the disease status table) following a "complete response." Distant recurrence was identified through a metastatic diagnosis date after the index date. Second primary nonbreast cancers were identified through appropriate International Classification of Diseases codes; squamous or basal cell skin cancers or new in situ carcinomas of any site were excluded. Time-to-event for iDFS and OS outcomes was calculated as time-from-index date to the first qualifying event (calculated with 30.4375 days per month). After we calculated the OS and iDFS using these definitions, we included patient data in the iDFS analysis only if their OS was equal to or exceeded their iDFS.

To establish the relationship between iDFS and OS, it is accepted that both time-to-event outcomes with censoring and rank correlation analysis are appropriate. We estimated the Spearman's correlation coefficient and used an iterative multiple imputation (IMI) algorithm. For IMI, a rank correlation coefficient ρ (similar to Spearman's coefficient) was assessed. R^2 was further calculated to explain the proportion of variability in OS accounted for by iDFS. The IMI method was used to estimate Spearman's correlation to account for censoring when analyzing IDFS-OS correlation and as an alternative to the maximum likelihood methodology for the normal copula approach; IMI has been proven to require a fraction of the computing time (≈0.05% of the copula approach) without affecting statistical performance.[22]

In addition to the overall EBC cohort, the relationship between iDFS and OS was analyzed for the following subgroups: ET (NSAI), tamoxifen [TAM] as first ET), menopausal status (premenopausal, postmenopausal), disease stage (stage II, III), nodal involvement (yes, no), prior (neo)adjuvant chemotherapy (yes, no), and prior radiotherapy (yes, no). If a patient was premenopausal with a record >365 days before the index date, or if the documented menopausal status was perimenopausal or missing, age ≥50 years was used as a proxy for determining menopausal status. Male patients were analyzed with premenopausal women. All confidence intervals (CIs) were reported as 95%.

The strength of the relationship between iDFS and OS was assessed using the following criteria for rank correlation coefficients: 0–0.19, very weak; 0.2–0.39, weak; 0.40–0.59, moderate; 0.6–0.79, strong; and 0.8–1, very strong.[23] In addition, we used a common threshold of clinically relevant surrogacy of $R^2 \geq 0.7$.[24]

RESULTS

Patient demographics and clinical characteristics

Of an initial 33,714 patients with a curated diagnosis of BC in the database (BC cohort), 3133 patients met all criteria to be included in the analysis as part of the final EBC cohort (Figure 1). Patients in the

BC cohort: patients with a curated diagnosis for BC
(n = 33,714)

Eligibility criteria	N	%
Non-missing sex and aged 18 years and older at initial diagnosis	32,057	95.1
Underwent surgery	25,927	76.9
Tested positive for estrogen receptor or progesterone receptor or both and negative for HER2	13,697	40.6
Diagnosed with stage II, IIA, IIB, or IIIA disease **or** stage III, IIIB, or IIIC disease, with a residual tumor status of 0	5,258	15.6
Treated with ≥1 qualifying adjuvant ET regimen	3,750	11.1
Had no record of metastatic disease if >1 staging entry prior to index date	3,321	9.9
Index date ≥ 6 months prior to end of data cut (April 30, 2021)	3,310	9.8
No assessment date prior to index date for recurrent tumor	3,306	9.8
No record of other concurrent invasive malignancy prior to index date	3,133	9.3

Final EBC cohort
(n = 3,133)

FIGURE 1 Patient attrition flow diagram. BC indicates breast cancer; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

EBC cohort had a mean age of 58.4 years (standard deviation [SD], 12.4) at the index date or date of ET initiation; 98.8% were female and 29.9% were premenopausal (Table S1). The majority had stage II disease (80.9% [2535/3133]) and had nodal involvement (57.3% [1766 among 3084 with data on nodal status]). Prior treatment included (neo)adjuvant chemotherapy (40.5%) and radiotherapy (48.8%). A total of 3084 (98.4%) patients received adjuvant ET (and had OS ≥ iDFS), among whom 2048 (66.4%) and 1036 (33.6%) were initially treated with an NSAI or TAM, respectively. Distribution of patients included by year (based on index date) is detailed in Table S2. In the overall population, there were 1103 total iDFS events (35.2%), with 2- and 5-year iDFS rates of 88.9% and 73.9%, respectively. There were 554 OS events (17.7%), with 2- and 5-year OS rates of 97.4% and 90.5%, respectively. The median follow-up for iDFS was 55.1 months, and the median follow-up for OS was 68.2 months.

iDFS-OS correlation: Overall EBC cohort

In the overall cohort, 3130 patients had OS ≥ iDFS and were included in the correlation analysis (Figure 2). Significant positive correlation between iDFS and OS was demonstrated by the Spearman (ρ = 0.88 [95% CI, 0.87–0.89]; $p < .0001$) coefficient. IMI ρ also demonstrated a significant positive relationship between iDFS and OS (0.83; $p < .0001$). The strength of correlation was "very strong" by previously defined criteria for rank correlation.[23] iDFS accounted for 82% of the variation in OS ($R^2 = 0.82$), which was above the threshold of a clinically relevant surrogate.

iDFS-OS correlation: Subgroup analyses

ET

In the EBC cohort, 3084 patients were included in the ET subgroup analysis ($n = 2048$ with initial NSAI, and $n = 1036$ with initial TAM). Spearman and IMI ρ demonstrated a significant positive correlation between iDFS and OS regardless of initial ET (Table 1; $p < .0001$ for all estimates in both groups), which satisfies criteria to be interpreted as very strong in both subgroups. R^2 was 0.85 and 0.73 for the NSAI and TAM subgroups, respectively, surpassing the threshold of clinically relevant surrogate.

Menopausal status, disease stage, and nodal involvement

A total of 3130 patients in the EBC cohort had available or imputed menopausal status data and had OS ≥ iDFS. Because of missing values for the menopausal status variable, values were imputed using age ≥50 years as a proxy in 33.45% of patients. The Spearman and IMI analyses showed a significant positive correlation, interpreted as very strong, between iDFS and OS for both premenopausal ($n = 936$)

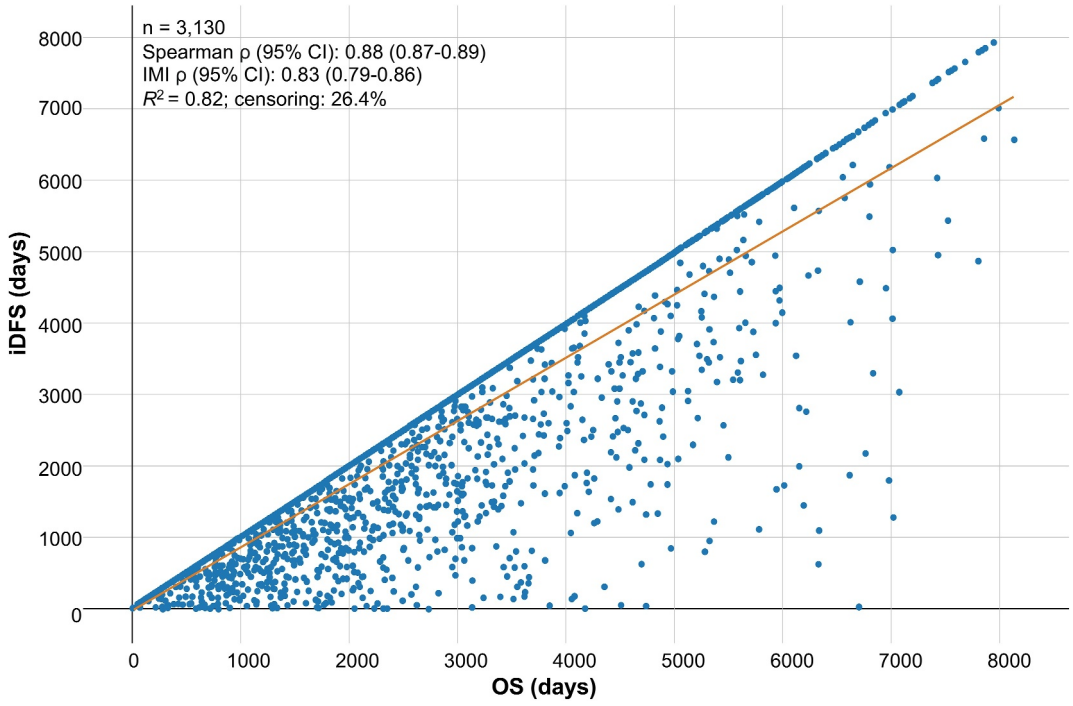

FIGURE 2 iDFS-OS correlation: overall cohort. iDFS indicates invasive disease-free survival; IMI, iterative multiple imputation; OS, overall survival.

and postmenopausal patients ($n = 2194$; $p < .0001$ for all estimates in both groups; Table 2). In the premenopausal and postmenopausal subgroups, 76% and 85% of the OS variability was explained by iDFS, respectively ($R^2 = 0.76$ and 0.85), confirming clinically relevant surrogacy.

Similarly, results among patients with stage II disease ($n = 2533$) or stage III disease ($n = 597$) were consistent with those in the overall population, showing significant, very strong, positive correlation between iDFS and OS for stage II and a strong positive correlation for stage III (Table 2; $p < .0001$ for all estimates in both subgroups); R^2 was 0.83 for stage II and 0.78 for stage III.

A total of 3084 patients had data on nodal status; 1766 had nodal involvement and 1318 had no nodal involvement. In both subgroups, there was a significant, very strong, positive correlation between iDFS and OS (Table 2; $p < .0001$ for all estimates in both groups); R^2 was 0.81 for patients with nodal involvement and 0.84 for those without nodal involvement.

Prior therapy

Results among patients with versus without prior (neo)adjuvant chemotherapy and with versus without prior radiotherapy were also consistent with those in the overall population. A total of 3130 patients had data on prior (neo)adjuvant chemotherapy (with prior [neo]adjuvant chemotherapy, $n = 1269$; without prior [neo]adjuvant chemotherapy, $n = 1861$). A significant, very strong, positive correlation between iDFS and OS was observed with or without prior (neo)adjuvant chemotherapy (Table 3; $p < .0001$ for all estimates in both groups); R^2 was 0.82 for both groups. Similarly, among patients with ($n = 1526$) and without ($n = 1604$) prior radiotherapy, iDFS was significantly and strongly positively correlated with OS (Table 3; $p < .0001$ for all estimates in both groups); R^2 was 0.82 for both groups.

DISCUSSION

The results from our study demonstrate a significant positive correlation between iDFS and OS in the adjuvant setting among a real-world population of patients with HR+/HER2– EBC. In the overall EBC cohort, the Spearman coefficient (ρ = 0.88 [95% CI, 0.87–0.89]; $p < .0001$) and IMI (ρ = 0.83 [95% CI, 0.79–0.86]) demonstrated a significant positive correlation with 82% of OS variation explained by iDFS ($R^2 = 0.82$). This correlation was also observed in all subgroup analyses conducted. Using previously established criteria for interpreting rank correlation, the overall EBC cohort analysis demonstrated a very strong correlation between iDFS and OS (i.e., 0.8–1) and also passed the threshold of clinically relevant surrogate ($R^2 > 0.7$). In subgroup analyses (ET, menopausal status, disease stage, nodal status, prior [neo]adjuvant chemotherapy, and prior radiotherapy), iDFS/OS correlation would also be classified as very strong in the vast majority of subgroups—the exception being in patients with stage III disease (IMI ρ = 0.79; "strong"), which was the

TABLE 1 ET: NSAI versus TAM subgroup analyses.[a]

	No.[b]	Spearman ρ (95% CI)	IMI ρ (95% CI)	R^2	Censoring, %
NSAI first	2048	0.89 (0.88–0.90)	0.83 (0.79–0.87)	0.85	27.0
TAM first	1036	0.87 (0.85–0.88)	0.81 (0.72–0.87)	0.78	25.7

Abbreviations: CI, confidence interval; ET, endocrine therapy; iDFS, invasive disease-free survival; IMI, iterative multiple imputation; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; TAM, tamoxifen.

[a]$p < .0001$ for all estimates.

[b]Number analyzed; patients with OS < iDFS were excluded.

TABLE 2 Menopausal status, disease stage, and nodal involvement subgroup analyses.[a]

	Subcriteria	No.[b]	Spearman ρ (95% CI)	IMI ρ (95% CI)	R^2	Censoring, %
Menopausal status	Pre	936	0.86 (0.84–0.88)	0.80 (0.70–0.87)	0.76	22.7
	Post	2194	0.89 (0.88–0.90)	0.84 (0.80–0.87)	0.85	28.0
Disease stage	II	2533	0.89 (0.88–0.90)	0.83 (0.79–0.87)	0.83	23.6
	III	597	0.84 (0.82–0.86)	0.79 (0.71–0.85)	0.78	38.2
Nodal involvement	Yes	1766	0.88 (0.87–0.89)	0.82 (0.77–0.85)	0.81	29.1
	No	1318	0.89 (0.88–0.90)	0.85 (0.79–0.89)	0.84	23.1

Abbreviations: CI, confidence interval; iDFS, invasive disease-free survival; IMI, iterative multiple imputation; OS, overall survival.

[a]$p < .0001$ for all estimates.

[b]Number analyzed; patients with OS < iDFS were excluded.

TABLE 3 Prior (neo)adjuvant chemotherapy and radiation therapy subgroup analyses.[a]

	Subcriteria	No.[b]	Spearman ρ (95% CI)	IMI ρ (95% CI)	R^2	Censoring, %
(Neo)adjuvant chemotherapy	Yes	1269	0.87 (0.86–0.89)	0.84 (0.78–0.88)	0.82	26.9
	No	1861	0.88 (0.87–0.89)	0.83 (0.78–0.87)	0.82	26.1
Radiotherapy	Yes	1526	0.89 (0.88–0.90)	0.84 (0.79–0.88)	0.82	27.0
	No	1604	0.87 (0.86–0.89)	0.82 (0.76–0.86)	0.82	25.8

Abbreviations: iDFS, invasive disease-free survival; IMI, iterative multiple imputation; OS, overall survival.

[a]$p < .0001$ for all estimates.

[b]Number analyzed; patients with OS < iDFS were excluded.

smallest subgroup ($n = 597$) with the most censoring (38.2%). In all subgroups, the R^2 was above 0.7, suggesting that iDFS is a clinically relevant surrogate.

In oncology, OS is the "gold standard" clinical trial end point. However, OS poses some challenges as an end point, such as requiring a longer follow-up period to detect sufficient events for analysis than iDFS.[1] Therefore, although iDFS is accepted as a clinically relevant and meaningful end point in clinical trials, including by regulatory authorities, there is growing interest in identifying and validating surrogate end points for OS in HR+/HER2− EBC to provide results in a shorter timeframe.[10–14] Our study adds to the body of knowledge showing that iDFS is a clinically relevant surrogate for OS, as it showed there was a very strong correlation in all categories that were tested, including varying ET treatment. This suggests that the use of iDFS in clinical trials is justifiable.

Prior meta-analyses have established the surrogacy of DFS for OS in colon, gastric, and non–small cell lung cancer, with R^2 ranging from 0.85 to 1.00 in analyses of their overall populations.[8,9,25,26] Additionally, a meta-analysis of RCTs in HER2+ EBC demonstrated patient-level correlation between DFS and OS, with a Spearman coefficient of 0.90, and a trial-level correlation between DFS and OS HR, with a R^2 of 0.75.[10] Our current results for iDFS/OS in HR+/HER2− EBC are within the range of previously reported DFS/OS surrogates in these other disease states where DFS surrogacy is accepted.

A previously reported study used RCT data to investigate the relationship between iDFS/DFS and OS in HR+/HER2− EBC.[12] The study used both trial level data identified from a literature review of RCTs as well as individual patient data from the phase 3 FACE trial. Trial-level and individual patient data approaches were considered to be parallel, with both demonstrating that DFS/iDFS was highly correlated with OS.[12] Our current real-world patient-level analysis supports and extends the results of the previous trial-level and individual patient data analyses from RCTs. Whereas the previous analyses had limitations due to heterogeneous reporting and use of DFS and iDFS as surrogate end points, our current real-world analysis was able to use adapted STEEP criteria and focus solely on iDFS—a standardized and accepted end point which is used in current EBC RCTs.[11] Additionally, using real-world data, this study focused on a specific patient population, namely those with stage II/III HR+/HER2− EBC who had ≥1 adjuvant ET regimen (current standard of care). Results from all these different and parallel approaches—trial-level RCT, individual patient data from RCT, and real-world analysis—consistently demonstrated the correlation of DFS/iDFS with OS and provide what is now a significant body of evidence supporting the surrogacy of these end points.

Relatively few studies have been conducted to assess surrogate oncology end points in real-world populations. Those that have been reported either did not focus on breast cancer (prostate cancer, non–small cell lung cancer, and colorectal cancer), or did not study EBC (metastatic BC).[23,27–29] To our knowledge, we have conducted the first real-world study of surrogate end points for HR+/HER2− EBC in an adjuvant setting and the first to specifically investigate iDFS and OS. Because surrogate end points need to be validated in each disease subtype, our study is an important contribution to the currently available evidence, which supports iDFS as a surrogate end point for OS in adjuvant HR+/HER2− EBC. Recently, phase 3 trials of CDK4/6i (NATALEE and monarchE) have demonstrated significant iDFS benefit in patients with HR+/HER2− EBC.[18,19] This analysis demonstrates that iDFS is a reliable surrogate for OS in HR+/HER2− EBC.

There are several limitations to our study. As with any correlation analysis, it is not possible to establish causality.[30] The real-world data used in this study were from ConcertAI Patient360, which is a US-based database that includes deidentified patient data from academic and community oncology clinics; there needs to be a better understanding of the generalizability of this database to the overall US population. Furthermore, both routine clinical practice and the patient population in a real-world setting may vary from country to country; therefore, future research is warranted to explore real-world data from different countries and/or a global perspective to confirm our findings. Another limitation is the time gap between iDFS as a primary end point and the maturity of OS events as an end point; confounding events that were not accounted for, such as post-progression treatments, may occur during this period, potentially impacting OS outcomes. Additionally, although the iDFS event categories used in this analysis were consistent with those of STEEP, this analysis used criteria adapted for use in real-world data that may not precisely align with those used in RCTs, potentially introducing heterogeneity in the results. However, the consistency of our results, compared with those of previously published individual patient data and trial-level data from RCTs, is supportive of our findings.[12] Additionally, although iDFS is an accepted end point in adjuvant BC trials, more-recent STEEP (2.0) criteria have suggested additional end points (e.g., invasive breast cancer–free survival) that can potentially be used as alternatives to iDFS, depending on the clinical trial

design.[11] Future studies to investigate the surrogacy of these alternative end points for OS may be warranted. Finally, 35% of patients who met the criteria for inclusion into the analysis had an iDFS event, which may be a higher rate than those observed in seemingly comparable patients with HR+/HER2− EBC in clinical trials. In our analysis, data on adherence and treatment discontinuation were limited; these factors may have impacted patient outcomes and were not accounted for. Care received outside of oncology clinics providing data to ConcertAI may not have been captured; this may have led to potential selection bias in the study. The real-world nature of the data (missing data, data quality, and human/technical errors) may have also impacted the analysis. Menopausal status was imputed using age ≥50 years as a proxy where menopausal status was missing (33.5% of patients); the imputed status may not reflect the actual menopausal status of these patients.

In conclusion, our real-world analysis demonstrated a very strong correlation between iDFS and OS for adjuvant treatment of patients with HR+/HER2− EBC. This is consistent with and supportive of results of prior studies and supports the use of iDFS as a reliable surrogate end point for OS. Taken together, these studies suggest that iDFS could be used as a primary end point for further clinical trials in an adjuvant HR+/HER2− EBC setting to reduce the length of primary completion of the study ahead of mature OS data and facilitate provision of innovative and effective therapies to patients sooner.

AUTHOR CONTRIBUTIONS

Stephanie L. Graff: Conceptualization and writing—review and editing. **Sara M. Tolaney**: Conceptualization and writing—review and editing. **Lowell L. Hart**: Conceptualization and writing—review and editing. **Pedram Razavi**: Conceptualization and writing—review and editing. **Wolfgang Janni**: Conceptualization and writing—review and editing. **Lee S. Schwartzberg**: Conceptualization and writing—review and editing. **Andriy Danyliv**: Conceptualization, methodology, and writing—review and editing. **Murat Akdere**: Conceptualization, methodology, and writing—review and editing. **Ilia Ferrusi**: Conceptualization, methodology, and writing—review and editing. **Rishi Rajat Adhikary**: Conceptualization, methodology, formal analysis, and writing—review and editing. **Joyce A. O'Shaughnessy**: Conceptualization and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

No new data was generated.

ORCID

Stephanie L. Graff https://orcid.org/0000-0003-1928-1722
Sara M. Tolaney https://orcid.org/0000-0002-5940-8671

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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