Association Between Invasive Disease–Free/ Distant Recurrence–Free Survival and Overall Survival in Patients with Early-Stage Triple-Negative Breast Cancer

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Background

- Although overall survival (OS) is a widely recognized indicator of clinical benefit,[1] extended follow-up periods are required to observe a sufficient number of events. This is particularly true for diseases such as early breast cancer (BC), where life expectancy has significantly increased due to improved treatments. Validated surrogate end points for OS can facilitate early assessment of treatment efficacy, aiding in accelerated regulatory and reimbursement approvals
- In this study, we aimed to evaluate surrogacy in patients with early-stage triple-negative BC (TNBC) who received neoadjuvant followed by adjuvant (perioperative) therapy. Specifically, we focused on assessing invasive disease–free survival (IDFS) or distant relapse–free survival (DRFS) as potential surrogates for OS in this early-stage population, as this relationship has yet to be established

Objective

- To evaluate the surrogate relationship between IDFS and DRFS or comparable end points, related with OS, among patients with early-stage TNBC

Methods

Methods for systematic literature review

- The systematic literature review (SLR) was conducted following the PRISMA guidelines[2] with searches conducted in MEDLINE®, Embase®, MEDLINE In-Process and the Cochrane Library (search date, December 4, 2023) and the Population, Intervention, Comparator, Outcome, and Study design (PICOS) are listed in **Table 1**. Included studies reported end points comparable to established definitions for IDFS and DRFS
- IDFS was defined time from date of randomization to the date of first invasive recurrence (local, regional, or distant), secondary invasive primary cancer (breast or not), or death due to any cause. Patients last known to be alive who have not experienced recurrence or second primary cancer are censored at their last contact date. DRFS was defined similarly, with only distant recurrences being considered

Table 1. PICOS criteria for review

Population	Adult patients with early TNBC (ER− , PR− , HER2− or ER− , PR− weakly positive and/or HER2− equivocal status)
Intervention	Any pharmacological adjuvant therapy
Comparator	Any pharmacological adjuvant therapy Placebo or best supportive care No restriction for noncomparative studies
Outcomes[a]	IDFS, DRFS, DDFS, DFS, EFS, RFS (if comparable), OS
Study Design	RCT, nonrandomized comparative studies, singlearm trials, prospective or retrospective observational studies, systematic reviews, meta-analyses or NMAs of clinical trials[b]

DDFS, distant disease–free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NMA, network meta-analysis; RCT, randomized controlled trial; RFS, recurrence-free survival.

[a]Definitions for IDFS or DRFS were reported in the comparator trials also as DFS, DRFS, DDFS, or RFS and thus these comparable outcomes were captured as their definition aligned with the pre-defined definitions of IDFS or DRFS.

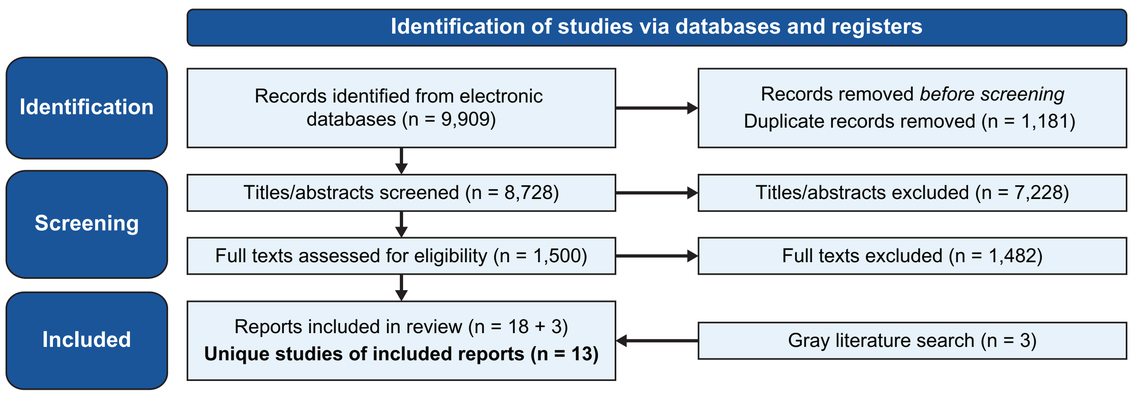
[b]For reference cross-checking only.

Methods for surrogate outcome analyses

- Trial-level and arm-level evidence was considered, based on published hazard ratios or landmark survival rates (reported or digitized from Kaplan-Meier curves), respectively
- Treatment arm-level reporting of landmark survival rates or the equivalent estimated from digitized Kaplan-Meier curves informed the feasibility surrogacy analyses
- Association between the relevant surrogacy end points and OS was estimated using unweighted, sample-weighted, and inverse variance-weighted linear regression models. With the goal of conducting the following analyses:
  - (1) Primary analysis of landmark survival rates between surrogacy end points and OS: 3-year surrogacy end points with 5-year OS; and (2) secondary analyses of 3-year surrogacy end points with 3-year OS, and 5-year surrogacy end points with 5-year OS
- Strength of association between surrogacy end points and OS was quantified using the coefficient of determination (R^2), and Pearson and Spearman's correlation coefficients (P), with bootstrapped 95% confidence intervals (CIs). Both correlation methods were included due to the small sample size of included studies, making normality assumptions difficult to assess
- Though there is no universally agreed upon threshold, following categorization used in other surrogacy assessments,[2] strength of correlation was defined as high for $P \geq 0.85$, moderate for $P > 0.7$ to $P < 0.85$, and low for $P \leq 0.7$

Results

Figure 1. PRISMA diagram



- A lack of data was found specifically for high-risk early stage TNBC patients. Thus, a broader study population was considered for analysis. Even when relaxing early-stage criteria, the evidence base remain limited
  - From 9,909 records (**Figure 1**), the SLR identified 13 unique studies.[3-15] Due to substantial differences in end point definition and/or lack of required data reported, 3 studies were excluded from all treatment arm-level surrogacy analysis (**Table 2**)
  - Ten studies reported IDFS or potentially equivalent end points (distant disease–free survival [DDFS], disease-free survival [DFS], event-free survival [EFS], and relapse-free survival [RFS]), but no study reported DRFS results only. Thus, assessment of DRFS as a surrogate end point was deemed unfeasible
- A lack of controlled studies prevented trial-level analysis requiring hazard ratios (HRs). Five studies (Bianco 2021,[3] Di Lisa 2023,[4] Promberger 2015,[8] Ferreira 2018,[10] and Shenoy 2021[12]) were single-cohort studies. Of the remaining 5 studies, only 3 reported HRs, thus trial-level surrogacy analysis requiring hazard ratios was not feasible
- Among the 10 studies reporting IDFS (or comparable end points), 3 studies were excluded from the base case and only were included in scenario analyses due to concerns about the comparability of end point definitions. IDFS or comparable end point definitions included DFS, IDFS, RFS, and EFS
- One study (Di Lisa 2023[4]) only reported 24 months DFS and thus did not contribute to 3-year or 5-year assessments and analyses
- The 4 studies with 5-year end point data reported a median follow-up time of 5.7 years for IDFS (or comparable end point) and 5.9 years for OS

Table 2. Studies considered for inclusion in surrogate outcome analysis

Study	Intervention	Sample size	Reported end point	Surrogate matching end point	Data available (3- and 5-yr)	Analysis inclusion
Studies reporting IDFS or potentially equivalent end points						
Bianco 2021[3]	NAC + Adj. CT	186	DFS	IDFS	Arm-level	BC,S
Di Lisa 2023[4,a]	NAC + Adj. Cape	270	DFS	IDFS	Arm-level	BC,S
Lynce 2024[5]	NAC + Adj. Nivo	15	IDFS	IDFS	Arm-level	BC,S
	NAC + Adj. Cape	15				
	NAC + Adj. Nivo and Cape	15				
Masuda 2017[6]	NAC: MR + Adj. Cape	139	DFS	IDFS	Study and arm-level	BC,S
	NAC: MR + Adj. Control	147				
Mayer 2021[7]	NAC + Adj. Cape	158	IDFS	IDFS	Study and arm-level	BC,S
	NAC+ Adj. cisplatin or carboplatin	148				
Promberger 2015[8]	NAC + Adj. CMF	28	EFS	IDFS	arm-level	BC,S
Schneider 2022[9]	NAC + genomically directed therapy	65	DFS	IDFS	Study and arm-level	BC,S
	NAC + treatment of physician choice	117				
Ferreira 2018[10]	NAC + Adj. docetaxel	41	DFS	IDFS	Arm-level	S
Dülgar 2022[11,b]	NAC + Adj. Cape	51	DFS	None	Arm-level	N
Shenoy 2021[12]	NAC + Adj. Adriamycin and cyclophosphamide	33	DFS	IDFS	Arm-level	S
Gamucci 2018[13]	NAC + Adj. anastrozole	77	DFS	IDFS	Arm-level	N
Li 2017[14]	NAC: PC or DO	90	RFS	IDFS	Arm-level	S
	NAC: CEF or NE	96				
Mittendorf 2020[15]	NAC + Adj. ET	165	DFS	IDFS	Arm-level	N

Adj, adjuvant; BC, base case; Cape, capecitabine; CEF, cyclophosphamide, epirubicin, 5- fluorouracil; CMF, cyclophosphamide and methotrexate and 5-fluorouracil; CT, chemotherapy; DO, docetaxel and oxaliplatin; ET, endocrine therapy; HR, hazard ratio; N, not included for any analysis; NAC, neoadjuvant chemotherapy; Nivo, Nivolumab; PC, paclitaxel and carboplatin; RCT, randomized controlled trial; S; scenario; yr, year.

[a]Di Lisa 2023 only reported the 24-month DFS; gray rows indicate studies excluded from analysis due to lack of comparable end point data.

[b]Dülgar 2022 DFS definition censored patients who die of a cause other than cancer, thus the outcome definition was not consistent with the IDFS definition.

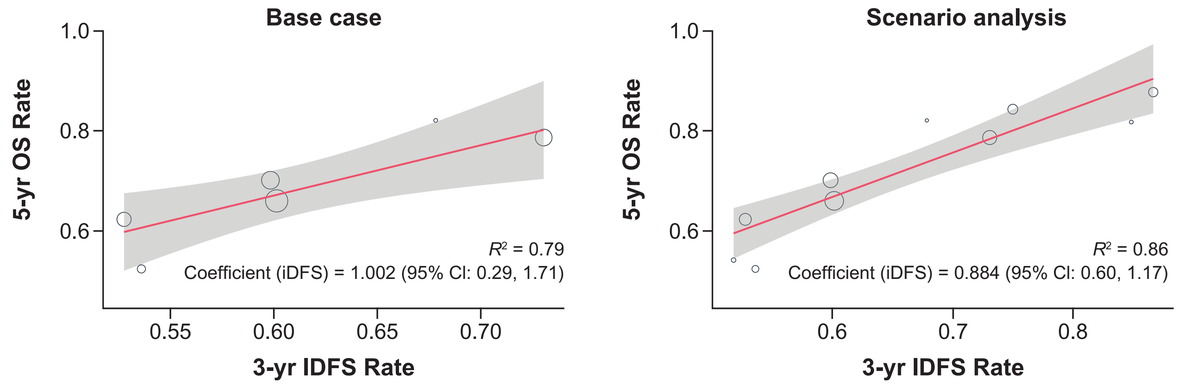
- Regardless of weighting method, moderate-to-high correlations were found between IDFS and OS for all timepoints (**Table 3**). Associated 95% CIs were found to be wide, due to the small number of studies and limited sample size in most studies
- Correlation estimates were higher in the scenario analysis, which included more studies (with more heterogeneity) compared to the base case analysis

Table 3. Summary of arm-level correlations for surrogacy associations[a]

Surrogacy assessment	Analysis	Model type	R^2 (95% CI)	Pearson (95% CI)	Spearman (95% CI)
3-year IDFS vs 5-year OS	**Base case**	**Sample weighted**	**0.79 (0.51, 1.00)**	**0.89 (0.71, 1.00)**	0.78 (-0.07, 1.00)
	Base case	Inverse variance weighted	0.81 (0.54, 0.99)	0.90 (0.72, 0.99)	0.79 (-0.11, 1.00)
	Base case	Unweighted	0.79 (0.52, 1.00)	0.89 (0.703, 1.00)	0.83 (0.00, 1.00)
	Scenario	**Sample weighted**	**0.86 (0.73, 0.95)**	**0.93 (0.85, 0.97)**	**0.91 (0.54, 1.00)**
3-year IDFS vs 3-year OS	Base case	Sample weighted	0.91 (0.50, 1.00)	0.95 (0.71, 1.00)	0.87 (0.33, 1.00)
5-year IDFS vs 5-year OS	Base case	Sample weighted	0.55 (0.06, 1.00)	0.74 (0.20, 1.00)	0.78 (-0.21, 1.00)

[a]Dark blue values indicate measures of strong correlation; light blue values indicate measures of moderate correlation; bolded rows indicate models that are presented graphically.

Figure 2. Arm-level associations for 3-yr IDFS and 5-yr OS (sample weighted)



Conclusions

- Limited evidence on IDFS, DRFS, and OS outcomes among patients with early-stage TNBC in the adjuvant setting challenges the ability to accurately quantify the surrogacy relationship between IDFS or DRFS with OS
- Lack of RCTs prevents the evaluation of surrogacy relationships to support level 1 (most robust)[16] evidence (which requires relative treatment effects from RCTs)
- Though end point definitions from studies included in the IDFS and OS arm-level correlation assessments were deemed comparable, the lack of consistency in surrogate end point definitions is a limitation
- Our analysis of treatment-arm landmark survival rates suggests IDFS (and identified comparable end points) as a potential surrogate for OS in the early-stage TNBC landscape, despite the small number of studies available. Future RCTs in this specific disease population could provide further insights to inform current surrogacy estimation findings
- Overall, the direction of slope and statistical significance between IDFS and OS were maintained, except in the analyses comparing 5-year IDFS vs 5-year OS

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