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Original Article

Characterization of real-world clinical and pathological differences between HER2-0 and HER2-low localized breast cancer

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ABSTRACT

Background: Recent studies suggest that breast cancer patients expressing low levels of human epidermal growth factor receptor 2 (HER2) may benefit from anti-HER2 therapy. Yet, the clinicopathological features of this novel subgroup, known as HER2-low, remain poorly characterized. The aim of this study was to characterize the differences between HER2-negative and HER-low patients.

Methods: This retrospective study included all new localized breast cancer cases diagnosed during 2019 in Southwest Finland. We identified 458 patients, of which 356 were HER2-negative. We further classified HER2-negative patients as follows: HER2 immunohistochemistry (IHC) 0 as HER2-0 and HER2 IHC 1+ or 2+ patients with no amplification by *in situ* hybridization as HER2-low.

Results: Out of the 378 HER2 non-amplified tumors, 26% ($n = 100$) were HER2-0 and 74% ($n = 278$) were HER2-low. Compared to HER2-0, HER2-low patients had fewer comorbidities ($p = 0.030$) and were more often diagnosed asymptomatically via screening ($p = 0.012$). HER2-low tumors exhibited lower histological grade ($p = 0.021$), higher hormone receptor (HR) expression levels (ER: $p = 0.0003$; PR: $p = 0.001$) and lower proliferation rates ($p = 0.005$) than HER2-0 tumors.

In HR+ patients, HER2-low was associated with superior OS in stage 2 ($p = 0.028$) and stage 2a disease ($p = 0.004$), as well as in patients with 1–2 metastatic lymph nodes (OS: $p = 0.006$, DFS: $p = 0.044$). Multivariable analyses performed in all stage 2a patients revealed that HER2-status remained an independent predictor of OS when adjusting for age (≥65 vs. <65 years), detection method, multifocality and administration of adjuvant radiotherapy.

Conclusion: HER2-low patients are characterized by beneficial clinical and pathological features that differ significantly from HER2-0 patients. In the HR+ population, HER2-low is associated with improved survival in breast cancer with locally advanced early-stage disease.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a receptor tyrosine kinase known to be overexpressed due to *ERBB2* gene amplification in 15–20% of breast cancer tumors [1,2]. Traditionally, the overexpression of HER2 has been associated with poor prognosis and aggressive disease. However, after the emergence of the first anti-HER2 therapeutic antibody over 25 years ago and the development of HER2-targeting tyrosine kinase inhibitors and antibody-drug-conjugates (ADC), the survival of HER2-positive patients has significantly improved [3–5].

The advancement of anti-HER2 therapies has emphasized the role of HER2 pathological diagnostics in determining available treatment options. Currently, HER2-expression is measured using immunohistochemical (IHC) assays and *in-situ* hybridization (ISH) as follows: IHC 0 and 1+ tumors are HER2-negative and IHC 3+ tumors are HER2-positive, leaving IHC 2+ tumors to be confirmed using ISH [6]. IHC 2+/ISH-negative tumors are classified as HER2-negative, while IHC 2+/ISH-positive tumors with gene amplification are HER2-positive, thereby enabling HER2-negative cancers to express heterogeneous

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levels of HER2. After the limitations of this binary classification were recognized, a novel subclass known as *HER2-low* emerged, composed of IHC 1+ and IHC 2+ tumors without amplification [7]. Approximately 40–50% of all breast cancer is HER2-low [8,9].

The development of anti-HER2 therapies facilitated the expansion of the HER2-targeted therapy frontier to the HER2-non-amplified patient population. Namely, the ADC trastuzumab deruxtecan (T-DXd) has demonstrated promising results in HER2-low metastatic breast cancer in the DAISY and DESTINY-Breast04 trials [10,11]. In the phase 2 DAISY trial, the confirmed objective response rates of hormone receptor-negative (HR-) and hormone receptor-positive (HR+) metastatic breast cancer were 37.5% in the HER2-low cohort and 29.7% in the HER2-negative cohort [11]. Similarly, in the phase 3 DESTINY-Breast04 trial, HR+ and HR-/HER2-low patients treated with T-DXd exhibited longer progression-free survival (PFS) and overall survival (OS), when compared to physician-selected chemotherapy [10]. These notable findings led T-DXd to be approved by the U.S. Food and Drug Administration (FDA) in 2022 and the European Medicines Agency (EMA) in 2023 for the treatment of unresectable and metastatic HER2-low breast cancer. The efficacy of T-DXd in HR+/HER2-low breast cancer has been further supported by the DESTINY-Breast06 trial; higher PFS was observed even among metastatic patients with ultralow HER2-expression (IHC 0 with membrane staining) following T-DXd administration after endocrine therapy, when compared to physician-selected chemotherapy [12]. As a result, the FDA and EMA approved T-DXd for the treatment of unresectable or metastatic HR+/HER2-low or HER2-ultralow breast cancer in 2025 [13]. The success of ADCs in metastatic disease has initiated investigations on the efficacy of T-DXd in an adjuvant treatment setting. For instance, the SURVIVE-HERoes aims to establish the efficacy of T-DXd in patients with intermediate to high-risk HER2-positive or HER2-low early breast cancer [14].

Despite the impressive activity in ADCs in metastatic HER2-low cancers and subsequent propositions to redefine HER2 classifications to also take into account non-amplified HER2-expressing cancers as an entity, the clinicopathological features of HER2-low breast cancer have yet to be unraveled. Studies have suggested that HER2-low and HER2-negative patients are two clinically distinct patient groups defined by unique characteristics and differing prognoses [15–18]. A meta-analysis involving approximately 600,000 early-stage breast cancer patients found that HR-/HER2-low tumors were associated with lower grade and smaller tumor size compared to HER2-negative tumors; the disease-free survival (DFS) and OS of HER2-low patients were also superior to HER2-negative patients in both the HR+ and HR- subgroups [18]. Likewise, a meta-analysis of 80,000 early-stage breast cancer patients noted superior survival outcomes in the HER2-low cohort compared to HER2-negative patients, regardless of HR status [16]. One study noted that HER2-low breast cancer was linked to fewer T4 tumors and negative lymphatic invasion in HR+ early breast cancer and lower proliferation in all HR subgroups [19]. Despite these findings regarding the differences between HER2-0 and HER2-low, a limited amount of real-world data that combines reliable data collection, sufficient follow-up duration and high-quality population-based data, such as that available within the Finnish healthcare system.

The aim of this study was to comprehensively characterize the differences in the real-world clinicopathological characteristics between HER2-low and HER2-negative breast cancers in the Finnish population, as well as to evaluate the prognostic differences between these two subgroups. In this study, we present detailed comparisons of HER2-low and HER2-negative breast cancer characteristics and clinical outcomes using high-quality manually collected real-world data from patients in Southwest Finland.

Patients and methods

Patient population

This retrospective study included all patients newly diagnosed with breast cancer in 2019 at the Turku University Hospital in the Wellbeing Services County of Southwest Finland (population of approximately 500,000 people). The baseline patient population is described in our earlier work [20]. This patient population was identified via Auria Clinical information services (Turku, Finland); patients with the International Classification of Diseases, 10th edition (ICD-10) breast cancer code C50 and/or metastasis codes C77, C78, C79 present in their health records from January 1, 2019, to December 31, 2019, were included in the study. Patients diagnosed with relapse of breast cancer in 2019 were excluded. The data of this baseline patient population was manually collected from electronic health records to avoid the potentially erroneous nature accompanied by automated collection of data. The patient selection process is described in Fig. 1. Patients with HER2-positive tumors (HER2 IHC 3+, IHC 2+ with ISH-amplification), missing a HER2-ISH result or HER2-status, stage 4 disease or those who received neoadjuvant chemotherapy were excluded. The study cohort was followed until February 2024, thus enabling the analysis of five-year survival rates and treatment outcomes.

Study design

The primary endpoint of this study was to compare the OS and DFS of patients with HER2-0 and HER2-low localized breast cancer. The secondary endpoint of the study was to identify differences in patient, tumor and treatment characteristics between HER2-0 and HER2-low disease.

Data collection

The data utilized in this research was retrospectively collected from electronic medical records of Turku University Hospital. Detailed information regarding the collected demographic and clinical data of patients, clinicopathological data of tumors and patient treatment data is provided in the supplementary material (Supplementary Table 1).

Statistical analysis

Categorical variables are summarized with counts and percentages (%). Normally distributed continuous variables are presented using means and standard deviations (SD), while non-normal continuous variables are presented using median and range. OS and DFS were used as endpoints in survival analyses. OS was defined as the time from the first oncological appointment to the date of death from any cause. DFS referred to the duration between first oncological appointment and the date of relapse (localized recurrence or metastasis), death from any cause or last follow-up. The end of the follow-up period, February 7th, 2024, was a censoring event in all survival analyses. Patients still alive at the end of the follow-up period were censored.

To study the association between two categorical variables, the Chi-square test was used unless its assumptions were not met; in such instances, Fisher's exact test was used. When comparing two normally distributed continuous variables, variance equality was assessed using Levene's test. Subsequently, the two sample *t*-test, either assuming equal or unequal variances, was used. For comparisons of two continuous non-normally distributed variables, the Wilcoxon rank sum test was used.

Survival curves were generated by using the Kaplan-Meier method. Univariate analyses were performed using the log-rank test and univariate Cox's proportional hazard model. Variables significant in the univariate analyses were chosen for further analysis via multivariable Cox's proportional hazards models. Correlation analyses were performed amongst these significant variables and strongly associated

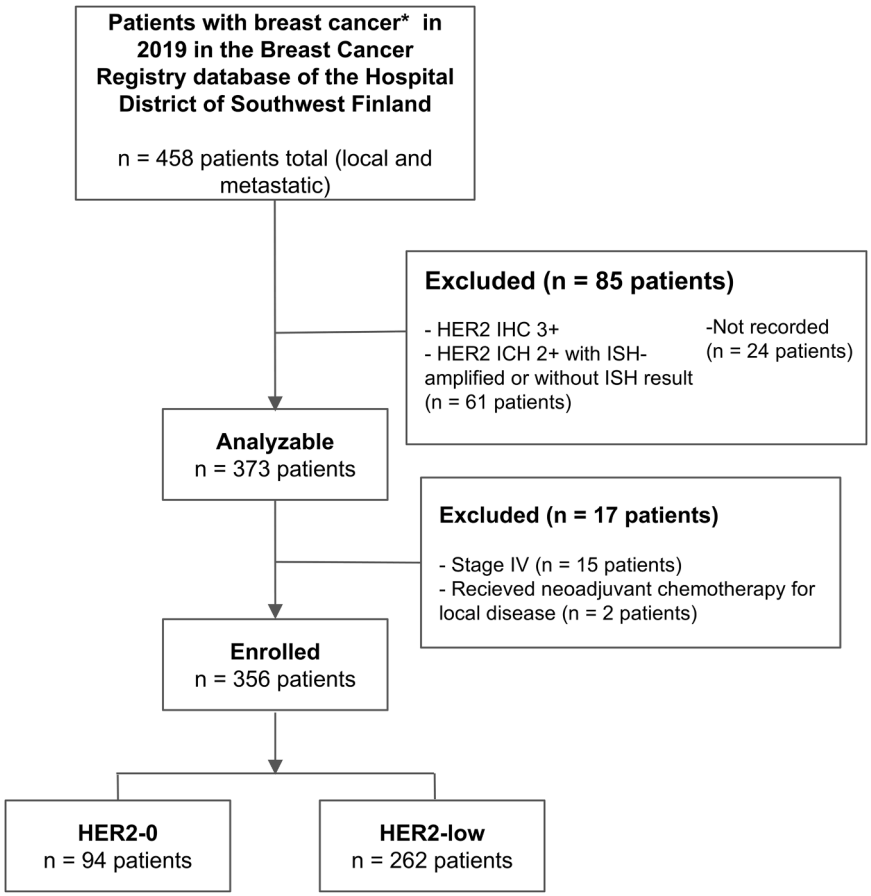

Fig. 1. Flow chart of study inclusion and exclusion criteria. * Not including DCIS or LCIS.

variables were excluded from multivariable analyses. Due to limited data size, models including a maximum of two explanatory variables were performed.

All statistical tests were two-sided, and the alpha level for determining statistical significance was set at 0.05. All statistical analyses were performed using JMP® software (version 17.0.0. SAS Institute Inc., Cary, NC, 1989–2024).

Results

Patient characteristics

A total of 458 patients were newly diagnosed with local or metastatic breast cancer at the Turku University Hospital in the Wellbeing Services County of Southwest Finland in 2019 [20]. In total, 356 patients were enrolled in this study (Fig. 1). Of these patients, 26% (n = 94) were HER2-0 and 74% (n = 262) were HER2-low.

The mean age of patients at diagnosis was 68 years (range 30–94 years) in the HER2-0 subgroup and 66 years (range 25–95 years) in the HER2-low subgroup. Nearly 90% of patients in both subgroups were postmenopausal. Approximately 20% of HER2-0 and HER2-low patients reported a family history of breast cancer, with mutations in breast cancer risk genes found in 2% (n = 2) of patients with HER2-0 disease. There were no significant differences in body mass index, age at menarche, menopausal age or status at diagnosis, parity, family history of breast cancer, BRCA-mutation status or Eastern Cooperative Oncology Group (ECOG) performance status between the two subgroups.

There was a significant difference observed in the Charlson Comorbidity Index (CCI)-scores of the HER2-0 and HER2-low subgroups (p = 0.030). The proportion of HER2-0 patients with a CCI-score of 0–2 points was 41% (n = 39), while 55% (n = 144) of HER2-low patients had a CCI-score of 2 or less. Similarly, 59% (n = 55) of HER2-0 patients had a CCI score of 3 or greater, whereas fewer than half of HER2-low patients exhibited a comparable CCI-score (n = 118, 45%). This significant difference was also observed in analyses comparing the average CCI of HR+ patients (p = 0.010).

The HER2-0 and HER2-low subgroups differed significantly in terms of detection methods (p = 0.012). Over half of HER2-0 patients were symptomatic at diagnosis, leading to breast cancer confirmed in subsequent imaging (n = 50, 53%), while the majority of HER2-low patients were diagnosed via screening mammography, with no prior symptoms (n = 153, 58%). Analyses in the HR+ population also displayed this significant difference when HR- patients were excluded (p = 0.019).

The demographic and clinical data of HER2-0 and HER2-low patients are described in more detail in Table 1.

Tumor characteristics

In analyses of histological grade, the proportion of grade 3 tumors in the HER2-0 subgroup (n = 24, 24%) was twice that of the HER2-low subgroup (n = 33, 12%), representing a statistically significant difference (p = 0.021). Histological subtypes did not differ significantly in analyses comparing HR+ HER2-0 and HER2-low patients (p = 0.44).

HR+/HER2-0 tumors were twice as likely to have micrometastases present in one lymph node (n = 14, 16%), compared to HR+/HER2-low tumors (n = 20, 8%) (p = 0.038).

HER2-0 was more often associated with triple negative breast cancer (TNBC) (p = 0.007), with the proportion of TNBC in the HER2-0 subgroup (n = 14, 14%) being nearly threefold higher than in the HER2-low subgroup (n = 14, 5%).

HER2-low breast cancer was associated with higher HR expression.

Table 1
Demographic and clinical data of HER2-0 and HER2-low patients.

	All patients (HR+ and HR-)					HR+ patients				
	HER2-0 (n = 94)		HER2-low (n = 262)		P-value	HER2-0 (n = 80)		HER2-low (n = 248)		P-value
Age at initial breast cancer diagnosis										
Median (range)	68	(30–94)	66	(25–95)	0.4006	68	(30–94)	66	(25–95)	0.2449
Sex, n (%)										
Female	94	(100)	262	(100)	1.00	80	(100)	248	(100)	1.00
Male	0	(0)	0	(0)		0	(0)	0	(0)	
BMI										
Average (SD)	27.8	(5.4)	27.0	(5.2)	0.2107	28.0	(5.6)	27.1	(5.2)	0.2048
Missing	7	(7)	9	(3)		6	(8)	8	(3)	
Menarche age										
Average (SD)	13.3	(1.8)	13.1	(1.4)	0.4176	13.3	(1.8)	13.1	(1.4)	0.3993
Missing	19	(20)	51	(19)		17	(21)	45	(18)	
Menopausal status at diagnosis, n (%)										
Premenopausal	12	(13)	28	(11)	0.5722	8	(10)	27	(11)	1.00
Postmenopausal	82	(87)	234	(89)		72	(90)	221	(89)	
Age at menopause median, (range)										
Average (SD)	49.5	(5.5)	49.5	(5.0)	0.942	49.3	(5.5)	49.7	(4.7)	0.5940
Missing	34	(36)	90	(34)		29	(36)	86	(35)	
Number of births										
Average (SD)	2.0	(1.2)	1.9	(1.2)	0.5968	2.0	(1.2)	1.9	(1.2)	0.4739
Missing	6	(6)	30	(11)		5	(6)	29	(12)	
Family history of breast cancer [a], n (%)										
No family history	60	(64)	178	(68)	0.5471	51	(64)	172	(69)	0.5545
Family history present	22	(23)	53	(20)		19	(24)	46	(19)	
Missing	12	(13)	31	(12)		10	(13)	30	(12)	
BRCA-mutation status, n (%)										
Genetic testing not performed	80	(85)	240	(92)	0.0546	70	(88)	228	(92)	0.4374
Genetic testing performed, but no breast cancer mutations were found	12	(13)	21	(8)		10	(13)	19	(8)	
Genetic testing performed, breast cancer mutation found [b]	2	(2)	0	(0)		0	(0)	0	(0)	
Genetic testing performed, mutation found that does not increase risk of breast cancer [c]	0	(0)	1	(0)		0	(0)	1	(0)	
Initial ECOG performance status, n (%)										
0	33	(35)	112	(43)	0.3631	27	(34)	106	(43)	0.3366
1	38	(40)	101	(39)		32	(40)	94	(38)	
2	14	(15)	23	(9)		13	(16)	23	(9)	
3	1	(1)	6	(2)		1	(1)	5	(2)	
4	0	(0)	1	(0)		0	(0)	1	(0)	
Missing	8	(9)	19	(7)		7	(9)	19	(8)	
CCI-score, n (%)										
0–2 pts	39	(41)	144	(55)	0.0302*	3.0	(1.8)	2.7	(1.7)	0.1536
≥ 3 pts	55	(59)	118	(45)		30	(38)	135	(54)	
Average (SD)	2.9	(1.8)	2.7	(1.7)	0.2703	50	(63)	113	(46)	0.0100*
Missing	0	(0)	0	(0)		0	(0)	0	(0)	
Breast cancer detection method, n (%)										
Patient symptomatic and cancer found in subsequent imaging	50	(53)	93	(35)	0.0121*	42	(53)	86	(35)	0.0194*
Found in screening mammography, no prior symptoms	40	(43)	153	(58)		34	(43)	147	(59)	
Found via examination by healthcare professional, no prior symptoms or imaging performed	4	(4)	16	(6)		4	(5)	15	(6)	
Missing	0	(0)	0	(0)		0	(0)	0	(0)	

Abbreviations: BMI, body mass index; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; HRT, hormone replacement therapy.
*=$p < 0.05$, **=$p < 0.01$.
[a] Definition of family history: mother, sister, daughter with invasive breast cancer.
[b] Genetic mutations found: BRCA1 (c.5266dup, p.(Gln1756Profs*74)), BRCA1 (c.68_69del, p.(Glu23Valfs*17)), BRCA2 (c.6996dup, p.(Val2333Cysfs*7)), ATM (c.3153 + 14T > A), PALB2 (c.1592del, p.(Leu531Cysfs*30)).
[c] Genetic mutation found: BRCA variant of unknown significance.

The median estrogen receptor (ER) -positivity of the HER2-low subgroup (98%, range 0–100%) was significantly higher than in the HER2-0 subgroup (95%, range 0–100%) ($p = 0.0003$). The median ER-positivity also significantly differed between these two subgroups in the HR+ subgroup (HER2-0: 95%, range 0–100%; HER2-low: 98%, range 2–100%; $p = 0.014$). Similarly, the proportion of ER-negative tumors was over three times greater in the HER2-0 subgroup ($n = 17$, 17%), compared to HER2-low tumors ($n = 14$, 5%), demonstrating a significant difference ($p = 0.0005$). This trend was also observed in analyses of progesterone receptor (PR) expression, as over a quarter of HER2-0 tumors were PR-negative ($n = 27$, 27%), compared to 12% ($n = 34$) in the HER2-low subgroup. ($p = 0.001$).

A significantly higher proportion of HER2-low tumors had a proliferation index ≤ 20% ($n = 219$, 79%), compared to HER2-0 tumors ($n = 64$, 64%) ($p = 0.005$). In the HR+ subgroup, 81% ($n = 214$) of HER2-low tumors had a proliferation index ≤ 20% compared to 73% ($n = 62$) in the HER2-0 cohort, but these results were not significant ($p = 0.13$).

The tumor size, focality, number of metastatic lymph nodes, number of lymph nodes with isolated tumor cells (ITC), lymphovascular invasion (LVI) status and stage did not significantly differ between the two groups.

The clinicopathological characteristics of HER2-0 and HER2-low tumors can be found in Table 2.

Table 2
Clinicopathological characteristics of HER2-0 and HER2-low tumors.

	All patients (HR+ and HR-)					HR+ patients				
	HER2-0 ($n = 100$)		HER2-low ($n = 278$)		*P*-value	HER2-0 ($n = 85$)		HER2-low ($n = 264$)		*P*-value
Histological subtype, n (%)										
Ductal	67	(67)	202	(73)	0.0857	56	(66)	188	(71)	0.4490
Lobular	17	(17)	53	(19)		17	(20)	53	(20)	
Mixed: ductal and other [a]	7	(7)	15	(5)		7	(8)	15	(6)	
Other [b]	9	(9)	8	(3)		5	(6)	8	(3)	
Missing/unknown	0		0			0	(0)	0	(0)	
Tumor size (mm), n (%)										
1–20mm	63	(63)	192	(69)	0.2106	55	(65)	184	(70)	0.3432
20+ mm	37	(37)	82	(29)		30	(35)	76	(29)	
Median (range)	15	(2–150)	15	(1.5–130)	0.7237	15	(2–150)	14	(1.5–130)	0.9008
Missing/unknown	0	(0)	4	(1)		0	(0)	4	(2)	
Focality, n (%)										
Unifocal	77	(77)	201	(72)	0.4281	64	(75)	190	(72)	0.6738
Multifocal	23	(23)	76	(27)		21	(25)	73	(28)	
Missing/unknown	0	(0)	1	(0)		0	(0)	1	(0)	
Histological grade, n (%)										
1	23	(23)	75	(27)	0.0205*	22	(26)	75	(28)	0.5077
2	53	(53)	168	(60)		52	(61)	164	(62)	
3	24	(24)	33	(12)		11	(13)	23	(9)	
Missing/unknown	0	(0)	2	(1)		0	(0)	2	(1)	
Number of all metastatic lymph nodes, n (%)										
Median (range)	0	(0–22)	0	(0–30)	0.3742	0	(0–22)	0	(0–30)	0.9536
0	71	(71)	180	(65)	0.1369	56	(66)	169	(64)	0.2181
1–2	17	(17)	72	(26)		17	(20)	70	(27)	
≥3	10	(10)	19	(7)		10	(12)	18	(7)	
Missing/unknown	2	(2)	7	(3)		2	(2)	7	(3)	
Number of metastatic sentinel lymph nodes, n (%)										
Median (range)	0	(0–3)	0	(0–4)	0.9488	0	(0–3)	0	(0–4)	0.5111
0	67	(67)	181	(65)	0.1369	54	(64)	170	(64)	0.8551
1–2	23	(23)	63	(23)		23	(27)	62	(23)	
≥3	1	(1)	3	(1)		1	(1)	3	(1)	
Missing/unknown	9	(9)	31	(11)		7	(8)	29	(11)	
Presence of micrometastases, n (%)										
No micrometastases	84	(84)	246	(88)	0.0634	69	(81)	232	(88)	0.0386*
Micrometastases present in one lymph node	14	(14)	20	(7)		14	(16)	20	(8)	
Micrometastases present in two lymph nodes	0	(0)	5	(2)		0	(0)	5	(2)	
Missing/unknown	2	(2)	7	(3)		2	(2)	7	(3)	
Number of lymph nodes with ITC, n (%)										
0	91	(91)	248	(89)	0.8754	76	(90)	236	(89)	0.8628
1	7	(7)	22	(8)		7	(8)	20	(8)	
2	0	(0)	1	(0)		0	(0)	1	(0)	
Missing/unknown	2	(2)	7	(3)		2	(2)	7	(3)	
LVI status, n (%)										
No LVI	59	(59)	140	(50)	0.2878	51	(60)	133	(50)	0.5049
LVI present	6	(6)	25	(9)		6	(7)	24	(9)	
Missing/unknown	35	(35)	113	(41)		28	(33)	107	(41)	
Biological subgroup, n (%)										
Triple negative	14	(14)	14	(5)	0.0070**					
HR+/HER2-	82	(82)	246	(88)		0	(0)	0	(0)	
Missing/unknown	4	(4)	18	(6)						
Hormone receptor status										
ER-positivity %, median (range)	95	(0–100)	98	(0–100)	0.0003**	95	(0–100)	98	(2–100)	0.0137*
ER-negative (0%), n (%)	17	(17)	14	(5)	0.0005**	2	(2)	0	(0)	0.0588
ER-positive (≥1%), n (%)	83	(83)	264	(95)		83	(98)	264	(100)	
Missing/unknown	0	(0)	0	(0)		0	(0)	0	(0)	
PR-positivity %, median (range)	80	(0–100)	85	(0–100)	0.1065	90	(0–100)	90	(0–100)	0.8116
PR-negative (0%), n (%)	27	(27)	34	(12)	0.0013**	12	(14)	20	(8)	0.0848
PR-positive (≥1%), n (%)	73	(73)	242	(87)		73	(86)	242	(92)	
Missing/unknown	0	(0)	2	(0)		0	(0)	2	(1)	
Proliferation [c], n (%)										
≤20%	64	(64)	219	(79)	0.0047**	62	(73)	214	(81)	0.1305
>20%	36	(36)	59	(21)		23	(27)	51	(19)	
Median (range)	12	(1–80)	12	(1–80)	0.0538	10	(1–75)	11	(1–80)	0.5323
Missing/unknown	0	(0)	0	(0)		0	(0)	0	(0)	
Breast cancer stage, n (%)										
I	51	(51)	145	(52)	0.9428	43	(51)	137	(52)	0.9904
IIA	30	(30)	73	(26)		24	(28)	70	(27)	
IIB	9	(9)	25	(9)		8	(9)	24	(9)	
IIIA	8	(8)	23	(8)		8	(9)	22	(8)	
IIIB	1	(1)	3	(1)		1	(1)	3	(1)	
IIIC	0	(0)	4	(1)		0	(0)	3	(1)	
IV	0	(0)	0	(0)		0	(0)	0	(0)	
Missing/unknown	1	(1)	5	(2)		1	(1)	5	(2)	

Abbreviations: ITC, isolated tumor cells; LVI, Lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation; HER2, human epidermal growth factor 2.
*=$p < 0.05$, **=$p < 0.01$.
[a] Other histological subtypes appearing alongside invasive ductal: lobular, apocrine, neuroendocrine, mucinous, micropapillary, solid papillary.
[b] Other histological subtypes: mucinous, tubular, solid papillary, medullary, tubulolobular, metaplastic.
[c] Measured using Ki-67 or MIB-1.

Treatment characteristics

Breast-conserving surgery (BCS) and sentinel node biopsy (SNB) were the most common types of breast cancer and lymph node surgery performed, with no significant differences observed in terms of surgical treatment between the HER2-0 and HER2-low subgroups (BCS $p = 0.79$; SNB $p = 0.84$).

HER2-low patients were slightly more likely to receive adjuvant chemotherapy, with 46% ($n = 120$) receiving adjuvant chemotherapy compared to 37% ($n = 35$) in the HER2-0 subgroup; however, this difference was not statistically significant ($p = 0.18$).

Approximately 80% of both subgroups received radiation therapy, with roughly 60% of HER2-0 and HER2-low patients receiving radiation only to the breast or mastectomy area.

The proportion of patients who received hormone therapy was similar in both subgroups ($p = 0.59$), with aromatase inhibitors and specifically letrozole being the most commonly used hormone therapy.

The surgical and adjuvant therapy characteristics for localized

Table 3
Surgical and adjuvant therapy characteristics of HER2-0 and HER2-low patients.

	All patients (HR+ and HR-)					HR+ patients				
Surgical treatment	**HER2-0 ($n = 94$)**		**HER2-low ($n = 262$)**		***P*-value**	**HER2-0 ($n = 80$)**		**HER2-low ($n = 248$)**		***P*-value**
Type of breast cancer surgery, n (%) [a]										
Mastectomy	37	(39)	94	(36)	0.7937	32	(40)	86	(35)	0.6713
Breast-conserving surgery	57	(61)	166	(63)		48	(60)	160	(65)	
No breast surgery performed	0	(0)	2	(1)		0	(0)	2	(1)	
Type of lymph node surgery [a]										
SNB	74	(79)	198	(76)	0.8381	62	(78)	188	(76)	0.7550
ALND	9	(10)	34	(13)		7	(9)	30	(12)	
SNB and ALND	9	(10)	21	(8)		9	(11)	21	(8)	
No axillary surgery performed	2	(2)	9	(3)		2	(3)	9	(4)	
Adjuvant treatment										
Chemotherapy										
Patients who received adjuvant chemotherapy, n (%)	35	(37)	120	(46)	0.1822	26	(33)	109	(44)	0.0891
Adjuvant chemotherapy received [b]										
Only Docetaxel [c]	20	(57)	70	(58)	1.00	16	(62)	64	(59)	1.00
Docetaxel-Capecitabine	2	(6)	1	(1)	1.00	0	(0)	0	(0)	
CEF or CE	29	(83)	102	(85)	1.00	23	(88)	94	(86)	1.00
Only Paclitaxel	0	(0)	1	(1)	1.00	0	(0)	1	(1)	1.00
Palbociclib	0	(0)	1	(1)	1.00	0	(0)	1	(1)	1.00
CMF	4	(11)	17	(14)	1.00	3	(12)	15	(14)	1.00
CEX	2	(6)	1	(1)	1.00	0	(0)	0	(0)	
Radiation therapy										
Patients who received radiation therapy, n (%)	77	(82)	209	(80)	0.7626	66	(83)	200	(81)	0.8696
Total Gy of fractionated radiotherapy given, n (%)					0.4031					0.3084
40.05 (2.67 Gy x 15)	29	(38)	97	(46)		23	(35)	92	(46)	
42.72 (2.67 Gy x 16)	16	(21)	33	(16)		13	(20)	32	(16)	
50 (2 Gy x 25)	26	(34)	69	(33)		24	(36)	66	(33)	
Other	6	(8)	10	(5)		6	(9)	10	(5)	
Radiation therapy target, n (%)										
Only breast/mastectomy area	46	(61)	130	(63)	0.8900	37	(58)	124	(62)	0.5567
Breast and axillary region	29	(39)	78	(38)		27	(42)	75	(38)	
Missing	2		1			2		1		
Boost radiation, n (%)										
Received boost radiation of the tumor bed	10	(13)	18	(9)	0.2623	6	(9)	16	(8)	0.7957
Did not receive boost radiation of the tumor bed	65	(87)	190	(91)		58	(91)	183	(92)	
Missing	2		1			2		1		
Hormone therapy										
Number (%) of patients who received hormone therapy	66	(70)	193	(74)	0.5892	65	(81)	192	(77)	0.5343
Type of hormone therapy used [b]**, n (%)**										
Selective estrogen receptor modulator: Tamoxifen	8	(12)	35	(18)	0.3383	8	(12)	35	(18)	0.3386
Aromatase inhibitors	60	(91)	175	(91)	0.8053	60	(92)	174	(91)	0.8051
Only letrozole	40	(67)	103	(59)	0.4578	40	(67)	102	(59)	0.4448
Only anastrozole	11	(18)	29	(17)		11	(18)	29	(17)	
Only exemestane	1	(2)	10	(6)		1	(2)	10	(6)	
More than one type of aromatase inhibitor used	8	(13)	33	(19)		8	(13)	33	(19)	
LHRH-analog: Procren depot	3	(5)	14	(7)	0.5735	3	(5)	14	(7)	0.5742

Abbreviations: CEF, cyclophosphamide, epirubicin, fluorouracil; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; CE, cyclophosphamide, epirubicin; CMF, cyclophosphamide, methotrexate, and fluorouracil; CEX, capecitabine, epirubicin, cyclophosphamide; HER2, human epidermal growth factor 2; Gy, Gray; LHRH, luteinizing hormone releasing hormone.
[a] Defined by the most invasive operation performed.
[b] Note: some patients received more than one treatment type.
[c] Refers to patients receiving docetaxel either as single-agent chemotherapy or as part of combination chemotherapy, e.g. docetaxel followed by CEF.

disease are described in Table 3.

Real-world survival outcomes

Follow-up data was available for all patients. The median follow-up time of HER2-0 and HER2-low patients was 53.8 months (range 12.3–61.0 months; mean 52.3 months) and 55.2 months (range 0.4–61.0 months; mean 53.0 months), respectively. In the HER2-0 subgroup, ≤7 relapses and 10 deaths were noted during the follow-up period, while there were 11 relapses and 22 deaths were recorded in the HER2-low subgroup. There were no significant differences noted in OS or DFS between HER2-0 and HER2-low or in comparisons of these subgroups in the TNBC and HR+ subpopulations.

In patients with stage 2a disease ($n = 95$), the OS of HER2-low patients was significantly higher than that of HER2-0 patients in both the HR+ subgroup and all patients (HR+: $p = 0.004$; all patients: $p = 0.012$) (Fig. 2). In the multivariable analyses of HR+ patients with stage 2a disease, HER2-status (HER2-low versus HER2-0) remained an independent predictor of OS when adjusting for detection method and administration of adjuvant hormone therapy. Similarly, multivariable analyses of all stage 2a patients showed that HER2-status remained independently associated with survival when adjusting for age (≥65 vs. <65 years), detection method, multifocality and administration of adjuvant radiotherapy. Similarly, in HR+ patients with stage 2 disease ($n = 117$), the OS of the HER2-low cohort was significantly higher than in the HER2-0 cohort ($p = 0.028$) (Fig. 2). HER2-status remained an independent predictor of OS in the stage 2 HR+ cohort when adjusting for detection method in multivariable analyses. No significant differences were noted in DFS between the HER2-0 and HER2-low populations when stratifying patients by stage. Although HER2-status was a significant predictor of survival in the multivariable analyses adjusting for the aforementioned variables, the significance of HER2-status was attenuated when adjusting for other variables (Supplementary Tables 2 and 3). Notably, ER status and histological grade were among the covariates contributing most to the attenuation of the association between HER2 status and overall survival in both stage 2 and stage 2a multivariable analyses.

In patients with 1 to 2 metastatic lymph nodes ($n = 81$), Kaplan-Meier analyses revealed that the OS and DFS of HER2-low patients were significantly higher than in HER2-0 patients in both the HR + subgroup and in all patients (HR+: OS $p = 0.006$, DFS $p = 0.044$; all patients: OS $p = 0.047$, DFS $p = 0.040$) (Fig. 3). However, Cox proportional hazards estimates were insignificant due to the low number of events in the subgroup of patients with 1–2 metastatic lymph nodes. Thus, multivariable analyses were not performed in this subgroup. Comparisons of OS and DFS in both the HR+ subgroup and in all HER2-0 and HER2-low patients with no metastatic lymph nodes or ≥ 3 metastatic lymph nodes did not produce significant results.

Discussion

HER2-expression has long been considered an integral biomarker in breast cancer diagnostics. Recent studies have shown that drugs targeting HER2 also have efficacy in advanced breast cancers expressing "low" amounts of this protein, sparking the need to elucidate the clinicopathological differences between HER2-low and HER2-negative patients [10,11]. In this study, we have analyzed a clinical cohort of breast cancer patients with comprehensively collected clinical information in Southwest Finland to characterize differences between HER2-0 and HER2-low disease. Our results demonstrated that HER2-low is associated with favorable clinical and pathological features that are distinct from those of HER2-0 patients.

Notably, our study found that HER2-low breast cancer patients were more often diagnosed asymptomatically via screening mammography, whereas HER2-0 patients more frequently presented symptomatically, with breast cancer diagnosed in subsequent imaging. This is a novel finding regarding breast cancer detection that has not, to our knowledge, been previously described. We also present previously unreported data regarding the higher proportion of lower CCI-scores in HER2-low patients. The observed association between detection in screening mammograms and lesser comorbidities in the HER2-low subgroup may be connected. Namely, it is possible that patients with higher CCI-scores experience increased burden from chronic illnesses and less willingness to participate in screening mammograms or routine check-ups, thus leading to underrepresentation of patients with high CCI-scores.

This study demonstrates that HER2-low breast cancer is associated with stronger HR expression, whereas HER2-0 tumors more frequently lack HR expression. These findings are consistent with previous studies. In a study of over 5000 HER2-negative patients with nonmetastatic breast cancer, HER2-low tumors were significantly more likely to be HR+ compared to HER2-0 tumors, with 90.6% of HER2-low tumors and 81.8% of HER2-0 tumors expressing HR [21]. These percentages are comparable to our finding that 88% of HER2-low tumors and 82% of HER2-0 tumors were HR+. This association between HR-expression and HER2-low tumors has also been previously reported [15,17,18,22,23]. Studies have also shown that TNBC was significantly more common amongst HER2-0 tumors, which is also aligned with our findings [15,21,23]. We also observed that HER2-low tumors were less likely to have high histological grade or high proliferation rates compared to HER2-0 tumors, which corresponds with previous findings [15,18,19,23]. This

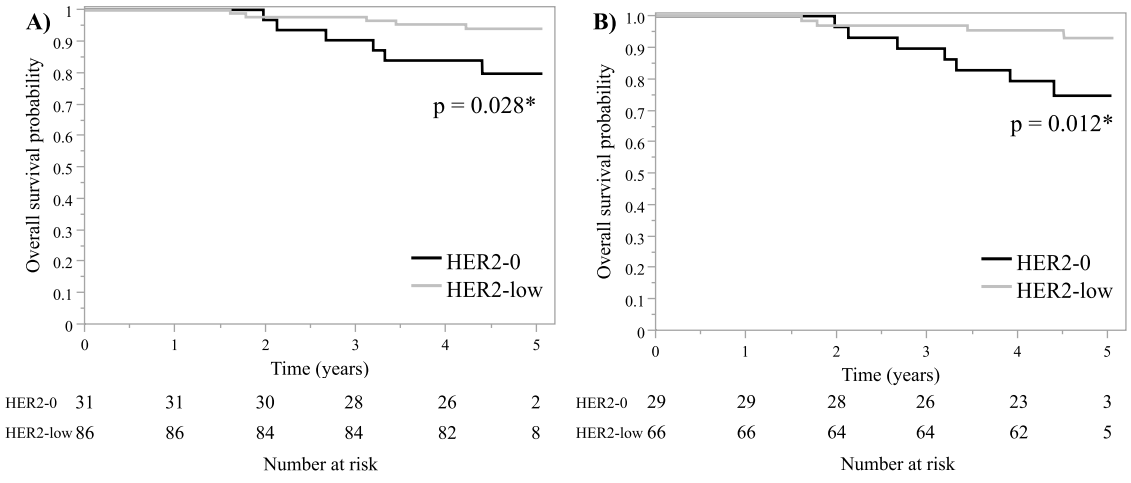

Fig. 2. Overall survival (OS) in stage 2(a) patients: (A) hormone receptor-positive HER2-0 vs HER2-low in stage 2 (a and b) disease; (B) all HER2-0 vs HER2-low patients in stage 2a disease. Numbers at risk reported at 0, 1, 2, 3, 4 and 5 years.

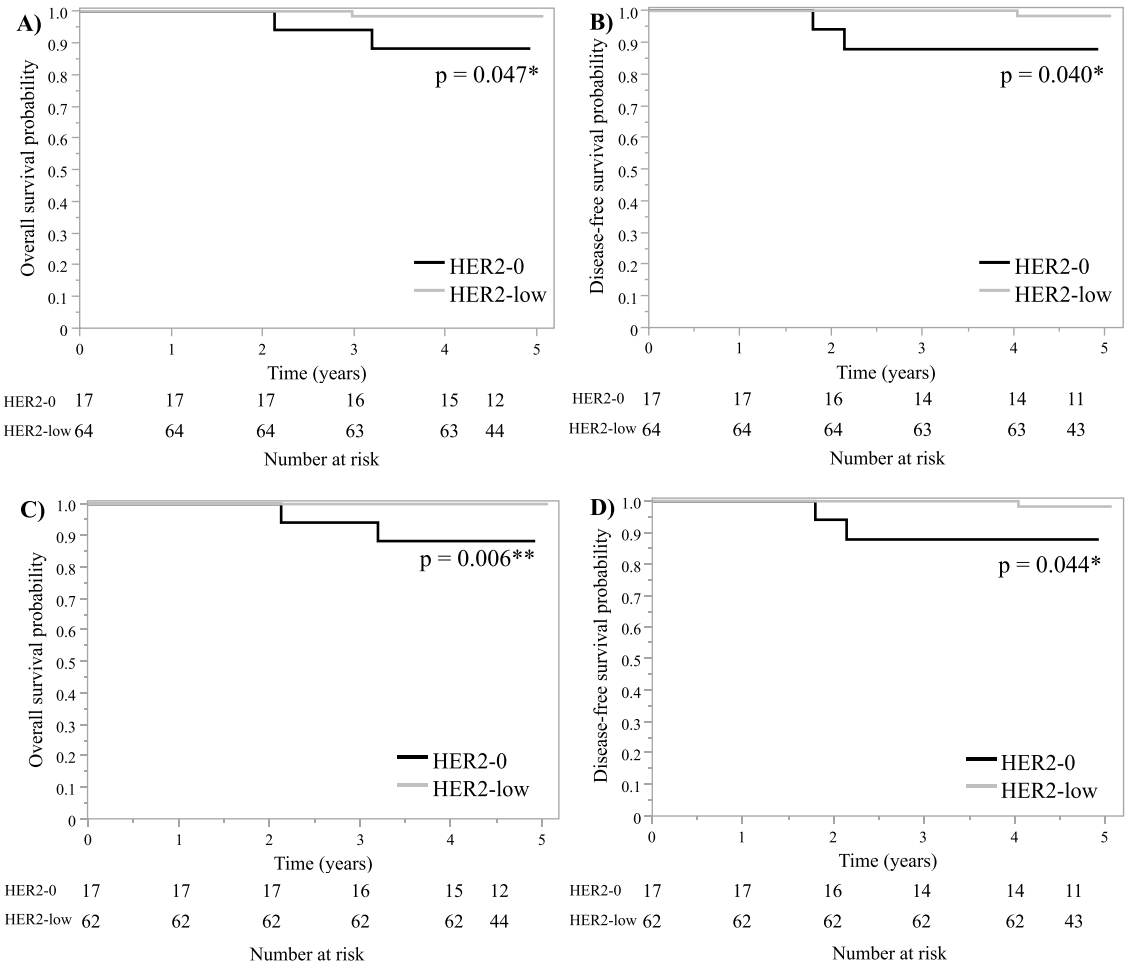

Fig. 3. Overall survival (OS) and disease-free survival (DFS) in patients with 1–2 metastatic lymph nodes: (A, B) all HER2-0 vs HER2-low patients; (C, D) hormone receptor-positive (HR+) HER2-0 vs HER2-low patients. Number at risk reported at 0, 1, 2, 3, 4 and 4.5 years due to all patients experiencing an event or being censored prior to the 5-year timepoint.

study provides previously unreported evidence on the beneficial pathological features associated with HER2-low breast cancer in the Finnish population.

Our study highlights novel data regarding real-world survival differences between HER2-0 and HER2-low breast cancer. In patients with stage 2a disease, OS was significantly greater in the HER2-low cohort compared to the HER2-0 cohort. This same trend was seen in the OS of HR+ patients with stage 2 disease. In multivariable analyses, HER2-status remained a significant independent predictor of OS in stage 2(a) disease in models containing clinicopathological and treatment-related variables, such as age, detection method and multifocality, as well as administration of radiotherapy and hormone therapy. However, HER2-status significance was attenuated when adjusting for other variables (Supplementary Tables 2 and 3), implying that the prognostic significance of HER2 may be confounded by these factors. Correspondingly, our study revealed that patients with 1 to 2 metastatic lymph nodes exhibited improved DFS and OS in both the HR+ and HR+/HR- HER2-low patients, when compared to their HER2-0 counterparts. It is likely that the remaining comparisons of lymph node-positive HER2-0 and HER2-low patients were insignificant due to small population sizes. In addition, the favorable prognosis of stage 1 breast cancer may explain the lack of significance; longer follow-up periods are needed to increase significance in such patient patients. This finding regarding the superior survival of HER2-low patients with 1 to 2 metastatic lymph nodes is a clinically compelling result, as this patient subgroup represents a borderline group in terms of breast cancer prognosis. Generally, lymph node negative patients are considered to have favorable prognoses, while patients with extensive lymph node involvement are often associated with adverse prognoses. Nevertheless, our findings suggest that HER2 expression lacking gene amplification may have prognostic relevance in localized breast cancer, but further studies are warranted.

Although some large meta-analyses have demonstrated superior survival in HER2-low patients compared to HER2-negative patients [16,18], several smaller studies have been unable to indicate significant differences in survival [17,19,21,22]. It is possible that the lack of survival differences between HER2-0 and HER2-low in these smaller studies may be due to the high survival rates and low likelihood of recurrence associated with HR+/HER2-low breast cancer. Studies including sizeable HR-/HER2-low populations have failed to demonstrate survival differences between HR-/HER2-low and HR-/HER2-0, despite providing evidence for survival differences in the HR+ subgroup [24,25]. It should be noted that the retrospective nature of this study led to imbalances in treatment administration, such as adjuvant chemotherapy, which may have implications on survival outcomes. Further research is warranted to elucidate the true differences in survival between the HER2-0 and HER2-low subgroups.

This retrospective study has various limitations. The majority of the pathological assessments of this study were done in 2019, a period when the distinction between IHC 0 and 1+ had no clinical implications. The pathological assessments of patient tumors were not reanalyzed for the sake of this study, which could lead to minor discrepancies in the results. The size of the patient population must also be considered when

interpreting these results. Although this dataset represents around 7% of nearly all annual breast cancer cases in Finland, multicenter studies are needed to be able to draw stronger conclusions about the nature of HER2-low breast cancer. Given that this study was restricted to patients with localized breast cancer who did not receive neoadjuvant therapy, the generalizability of our findings is limited to this population consisting of predominantly HR+ postmenopausal patients, as this is the common breast cancer patient population in Finland.

Conclusion

Our real-world retrospective study supports the assertion that HER2-low breast cancer is characterized by unique, beneficial characteristics that differ significantly from HER2-0 tumors. Lower histological grade, higher hormone expression levels and reduced proliferation are all favorable features that differentiate HER2-low from HER2-0. HER2-low tumors are also connected to superior survival in patients with 1 to 2 metastatic lymph nodes or stage 2 disease. Understanding the clinicopathological features of HER2-low breast cancer is essential, especially in an era of novel HER2-targeted therapies.

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Ethical approval

The study was approved by the Hospital District of Southwest Finland institutional research board (License numbers T781/2023; VSSHP/2023/136140). Informed consent was waived due to retrospective design of the study according to Finnish act on Secondary Use of Social and Health Data effective from April 2019 (Act 552/2019). All data were collected, stored, and handled in a manner that meets the regulation of GDPR and the Secondary Use Act 552/2019. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions and regulations mandated by the Secondary Use Act.

CRediT authorship contribution statement

Milla Hollmén: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Eliisa Löyttyniemi:** Writing – review & editing, Resources, Methodology, Formal analysis. **Eeva Juhanoja:** Writing – review & editing, Validation. **Pia Vihinen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Maria Sundvall:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

PV has received consulting or advisory honoraria from Merck, Bristol-Myers Squibb, Ipsen, Novartis, and Roche and speakers' bureau honoraria from Merck, Roche, and Bristol-Myers Squibb.

MS has received support to participate in educational events and conferences from Astellas, Amgen, Bayer, BMS, Daiichi-Sankyo, Gilead, Lilly, MSD, Novartis, Pfizer, Roche and received lecture or consulting/advisory honoraria from Amgen, Astellas, Astra Zeneca, Bayer, BMS, Daiichi-Sankyo, Exact Sciences, Gilead, MSD, Novartis, Roche and Stemline Therapeutics.

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MH and EL have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2026.101204.

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