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Original Research

Pathological complete response rate and disease-free survival after neoadjuvant chemotherapy in patients with HER2-low and HER2-0 breast cancers

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Abstract ***Background:*** Half of HER2-negative breast cancers (BC) show HER2-low expression. The strong efficacy of recent anti-HER2 antibody–drug conjugates (ADC) in HER2-low tumours has risen the interest of HER2-low as a proper BC subtype. Chemosensitivity and prognosis of this subtype are not clear when compared to HER2-0 tumours. We investigated the pathological complete response (pCR) and disease-free survival (DFS) rates in BC patients receiving neoadjuvant chemotherapy for HER2-low or HER2-0 tumours.
Methods: Data were collected from the Institut Paoli-Calmettes database. HER2-low tumours were defined by HER2 IHC score of 1+ or 2+ with negative FISH, and HER2-0 by IHC score of 0. Clinicopathological characteristics, pCR (defined as [ypT0/ypTis] and [pN0sn or ypN0]) and DFS rates were compared between the two cohorts.
Results: From Jan/2005 to Jun/2021, 1111 patients receiving neoadjuvant chemotherapy were evaluable. The incidence of HER2-low was 41%, including 63% of hormone receptor (HR)-positive and 37% of HR-negative tumours ($p < 0.001$). In the whole population, the pCR rate

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was lower in HER2-low (23%) versus HER2-0 (30%) tumours (p = 0.013), but this association was lost in multivariate analysis. In HR-positive patients, HER2-low negatively impacted pCR rates when compared to HER2-0 (10% *vs.* 16%, p = 0.046), but not in HR-negatives (46% *vs.* 42%), and this result was maintained in multivariate analysis. No correlation existed between DFS and HER2-status.

Conclusion: HER2-low is associated with HR positivity. HER2 status did not impact pCR in HR-negative patients, whereas HER2-low was associated with lower pCR rate in HR-positive patients.

1. Introduction

Until recently, the Human Epidermal growth factor Receptor 2 (HER2) status of breast cancers (BC) was considered in clinical routine as HER2-negative (80%–85% of cases) or HER2-positive (15%–20%) [1]. Only patients with HER2-positive tumours were candidate to anti-HER2 therapies that changed the natural course of early and metastatic BC. Among HER2-negative tumours, approximately 50% are categorised as HER2-low, defined as immunohistochemically (IHC) 1+ or 2+ and lack of HER2 gene amplification measured by *in situ* hybridisation, and 50% are categorised HER2-0, defined as IHC 0 [2–4]. In contrast to HER2-positivity, the clinical significance of a low-level expression of HER2 is unclear with conflicting results existing about its prognostic significance [4–8]. In daily practice, these tumours are reported as HER2-negative, either TNBC if hormone receptors (HR) are not expressed or luminal-like if expressed. However, the rise of HER2-low as a proper BC subtype is being accelerated by the results of clinical trials using novel antibody–drug conjugates (ADCs) such as trastuzumab deruxtecan and trastuzumab duocarmazine [9–12]. Indeed, these drugs showed antitumour efficacy in patients with HER2-low BC as well as in those with HER2-positive tumours. The strong efficiency of these drugs in the advanced setting results in defining HER2-low as a clinically relevant predictive biomarker and might represent a strategical axe of development in early BC, including in the (neo)adjuvant setting. Therefore, clarifying whether HER2-low early breast cancer (eBC) should be considered as an individual biological entity with distinct behaviour and prognosis and different sensitivity to standard chemotherapy is needed.

In this study, we compared the pathological response and disease-free survival rates in eBC patients treated with neoadjuvant chemotherapy (NAC) for HER2-low versus HER2-0 tumours.

2. Materials and methods

2.1. Patient selection and study design

Medical records of eBC patients treated from January 2005 to June 2021 were retrieved from clinical databases of Paoli-Calmettes Institute (Comprehensive Cancer Center of Marseille, France) for retrospective analysis. This cohort study was approved by our institutional review board (Registered study in Clinical research Department of Paoli Calmettes Institute: NAC-TS-IPC 2021-026). Selection criteria: women, age >18 years, initial diagnosis of invasive eBC, HER2-low or HER2-0 status, no metastasis at diagnosis, treatment with anthracycline and taxane-based NAC followed by surgery, documentation of pathological response on the operative specimen, and available follow-up. A total of 1111 patients fulfilling these criteria were included in the present study. Patient and tumour characteristics, treatments, and pathological results were collected. The patients had been staged using clinical examination, mammography, ultrasonography, and breast MRI, and PET-scan or a combination of CT-scan and bone scan. Evaluation of lymph node status was determined by sentinel lymph node biopsy (SLNB) with or without completion of axillary lymph node dissection (ALND) or only ALND. The method used for the detection of SN was a combined technique or isotopic only detection during the last years. All patients received either conventionally scheduled or intensified dose-dense anthracycline–taxane-based neoadjuvant chemotherapy. None of these patients had received trastuzumab or endocrine therapy in the neoadjuvant setting. Pathological complete response (pCR) was defined as [ypT0 or ypTis] and [pN0sn or ypN0] [16]. Hormonal Receptor (HR) status was determined according to the French guidelines (oestrogen and/or progesterone receptors by IHC with a 10% threshold for HR-positivity) [17]. HER2 evaluation was determined on biopsy specimen before neoadjuvant treatment by board-certified breast cancer pathologists using the ASCO/CAP guidelines [1]. HER2-low was defined as IHC 1+ or IHC 2+ and lack of HER2 gene amplification measured by *in situ* hybridisation. HER2-0 was defined as IHC 0.

2.2. Statistical analysis

Descriptive statistics were used to describe the categorical (counts and frequencies) and continuous (median and range) variables and compared by using $\chi 2$ tests. The primary endpoint was the pathological response to

NAC (pCR or no pCR). HER2 status (HER2-low *vs.* HER2-0) and pathological response rates (pCR *vs.* no pCR) were categorised and association with other variables was explored in univariate analysis by binary logistic regression. The multivariate analyses (binary logistic regression) tested the variables significant in univariate analysis. Follow-up was estimated by using the inverse Kaplan–Meier method. The survival endpoint was disease-free survival (DFS), defined as the time from surgery to any kind of invasive BC relapse (local or distant) or death from any cause. Survival curves were estimated using the Kaplan–Meier method and a 2-sided log-rank test was used to compare results between groups. Patients without events were censored at the time of last follow-up. Analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, Illinois) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of patients according to HER2 status

Of 1111 patients included, 456 (41%) had HER2-low tumours and 655 (59%) HER2-0 (Fig. 1). The HR-positivity was overrepresented in the HER2-low group compared to the HER2-0 group (63% *vs.* 45%; $p < 0.001$) (Table 1). In univariate analysis, the HER2-low status was also associated with tumour grade with less grade 3 than the HER2-0 status (47% *vs.* 53%; $p < 0.008$). No statistical difference was observed for the patients' age, clinical T and N stages, pathological type, type of mammary surgery, or type of surgical axillary exploration. In a binary logistic regression including HR status and SBR grade, HER2-low remained independently associated with HR-positivity (OR 2.12 [95 CI 1.62–2.78]; $p < 0.001$), but not with grade (Supplementary Table 1).

3.2. Pathological response to NACT in the whole population

A pathological complete response rate was reported in 305 patients (27%). In univariate analysis, achievement of pCR was associated with all the tested variables, including younger patients' age, HR-negativity, higher grade, lower clinical T and N stages, conservative surgery and SLNB, and HER2-0 status (Table 2). The pCR was obtained in 30% of patients with HER2-0 tumours versus 23% in HER2-low ($p = 0.013$). Among HER2-low patients, those with HER2-low 1+ versus 2+ scores had similar pCR (24% and 23% respectively) (Fig. 2A). In multivariate analysis, the HER2 status was no longer associated with pCR (OR 0.91 [95 CI 0.67–1.24]; $p = 0.559$), whereas HR-positivity, age between 50 and 74 years, cT3 stage, cN ≥ 1 stage, and grade 3 remained independently associated with pCR (Table 3). Similar results were obtained when using HER2 status as a multi-nominal variable including HER2-0, HER2-low 1+, and HER2-low 2+ categories (Supplementary Table 2).

3.3. Pathological response to NACT in HR-positive BC

Among the 583 patients with HR-positive tumours, 289 (50%) had a HER2-low phenotype and 294 (50%) were HER2-0. A pathological complete response rate was reported in 77 patients (13%). In univariate analysis, achievement of pCR was associated with HER2 status (10% in HER2-low patients *vs.* 16% in HER2-0; $p = 0.046$) (Fig. 2B), younger age, and higher grade (Supplementary Table 3). In a binary logistic regression including these three variables, the HER2-low status remained independently associated with lower pCR rates (OR 0.60 [95 CI 0.36–1.00]; $p = 0.049$) (Supplementary Table 3), as did patients' age and grade.

3.4. Pathological response to NACT in HR-negative BC

Among the 528 patients with HR-negative tumours, 167 (32%) had a HER2-low phenotype and 361 (68%) a HER2-0 phenotype. A pathological complete response rate was reported in 228 patients (43%). In univariate analysis, pCR was not significantly associated with HER2 status (46% in HER2-low patients *vs.* 42% in HER2-0; $p = 0.356$) (Fig. 2C), but associated with cT stage, grade, and axillary procedure type (Supplementary Table 4). In a binary logistic regression

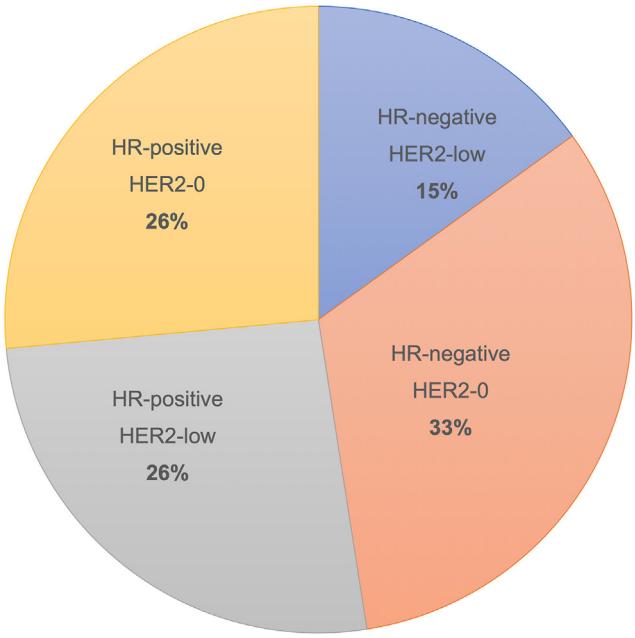

Fig. 1. Distribution of the study population according to hormone-receptors and HER2 expression.

Table 1
Clinicopathological characteristics of 1111 patients and tumours and correlations with the HER2 status.

		Total		Her2-0		HER2-low (1+ and 2+)		*p-value (Khi²)*
		n	%	n	%	n	%	
Age, years	≤40	252	23%	150	23%	102	22%	0.938
	41–49	289	26%	174	27%	115	25%	
	50–74	529	48%	307	47%	222	49%	
	≥75	41	4%	24	4%	17	4%	
cT stage	cT0-1	167	15%	104	16%	63	14%	0.382
	cT2	631	57%	371	57%	260	57%	
	cT3	245	22%	146	22%	99	22%	
	cT4	68	6%	34	5%	34	7%	
cN stage	cN0	535	48%	324	49%	211	46%	0.355
	cN ≥ 1	557	50%	318	49%	239	52%	
	Unknown	19	2%	13	2%	6	1%	
Pathological type	Ductal	817	88%	490	89%	327	87%	0.463
	Lobular	47	5%	27	5%	20	5%	
	Other	65	7%	34	6%	31	8%	
Grade	Unknown	40	4%	31	5%	9	2%	0.008
	1	66	6%	38	6%	28	6%	
	2	446	40%	241	37%	205	45%	
	3	559	50%	345	53%	214	47%	
Hormone receptor (HR) status	HR-positive	583	52%	294	45%	289	63%	<0.001
	HR-negative	528	48%	361	55%	167	37%	
Breast surgery	Conservative	530	48%	326	50%	204	45%	0.098
	Mastectomy	581	52%	329	50%	252	55%	
Axillary surgery	SLNB	247	22%	154	24%	93	20%	0.381
	ALND	686	62%	394	60%	292	64%	
	SLNB + ALND	178	16%	107	16%	71	16%	

Table 2
Associations of clinicopathological variables and pCR in univariate analysis.

		Total	pCR		no pCR		*p-value (Khi²)*
			n	%	n	%	
All patients		1111	305	27%	806	73%	
HER2 status	HER2-0 (0+)	655	198	30%	457	70%	0.045
	1+	209	50	24%	159	76%	
	2+	247	57	23%	190	77%	
	HER2-low[a]	456	107	23%	349	77%	0.013
Age, years	≤40	252	88	35%	164	65%	0.008
	41–49	289	83	29%	206	71%	
	50–74	529	125	24%	404	76%	
	≥75	41	9	22%	32	78%	
Hormone receptor (HR) status	HR-positive	583	77	13%	506	87%	<0.001
	HR-negative	528	228	43%	300	57%	
cT stage	cT0-1	167	51	31%	116	69%	0.005
	cT2	631	192	30%	439	70%	
	cT3	245	47	19%	198	81%	
	cT4	68	15	22%	53	78%	
Grade	Unknown	40	27	68%	13	33%	<0.001
	1	66	3	5%	63	95%	
	2	446	65	15%	381	85%	
	3	559	210	38%	349	62%	
cN stage	cN0	535	176	33%	359	67%	<0.001
	cN ≥ 1	557	124	22%	433	78%	
	Unknown	19	5	26%	14	74%	
Surgery	Conservative	530	168	32%	362	68%	0.002
	Mastectomy	581	137	24%	444	76%	
Axillary	SLNB	247	110	45%	137	55%	<0.001
	ALND	686	151	22%	535	78%	
	SLNB + ALND	178	44	25%	134	75%	

[a] Her2 low versus Her2 = 0.

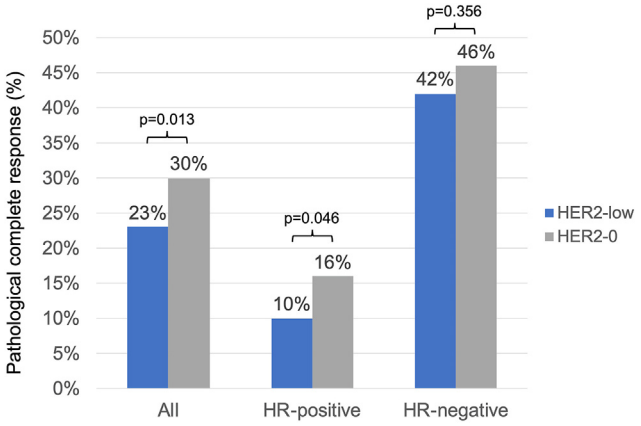

Fig. 2. pCR rates according to HER2 status in all, HR-positive, and HR-negative patients.

including these three variables in addition to HER2 status, HER2-low status was not independently associated with pCR (OR 1.15 [95 CI 0.77–1.71]; p = 0.490) (Supplementary Table 4).

3.5. Disease-free survival according to HER2 status in the whole population

Of 817 patients with survival data, 493 were HER2-0 and 324 were HER2-low. With a median follow-up of 73 months [95 CI 70.3–76.8], the 3-year DFS was 81% [95 CI 78.3–83.7] in the whole population. As expected, patients with pCR had longer 3-year DFS than patients without pCR (93.6% [95 CI 90.2–97.0] *vs.* 76.9% [95 CI 73.6–80.2]; log-rank test p < 0.001) (Supplementary Fig. 1). Patients with HER2-0 and HER2-low tumours had similar 3-year DFS (80% [95 CI 76.5–83.5] *vs.* 82.4% [95 CI 78.2–86.6]; log-rank test p = 0.742) (Supplementary Fig. 2). The same analysis was done by separating the patients with versus without pCR. No difference was observed between the HER2-0 and HER2-low groups in term of 3-year DFS in the patients who achieved pCR (92.7% [95 CI 88.2–97.2] *vs.* 95.3% [95 CI 90.3–100]; log-rank test p = 0.821), nor in the patients without pCR (75.6% [95 CI 71.2–80.0] *vs.* 78.9% [95 CI 73.9–83.9]; log-rank test p = 0.921) (Fig. 3A).

3.6. Disease-free survival according to HER2 status in HR-positive and NR-negative patients

The same observation existed according to the HR status. In the HR-positive patients, no difference in 3-years DFS was observed between HER2-0 and HER2-low patients in the pCR group (92.9% [95 CI 85–100] *vs.* 94.1% [95 CI 82.6–100]; log-rank test p = 0.511), and in the no pCR group (83.4% [95 CI 78.5–88.3] *vs.* 83.9% [95 CI 78.7–89.1]; log-rank test p = 0.597) groups (Fig. 3B). In the HR-negative patients, the 3-years DFS was not different between HER2-0 and HER2-low patients in the pCR (92.4% [95 CI 86.8–97] versus 95.6% [95 CI 89–100]; log-rank test p = 0.622), and in the no pCR (63% [95 CI 55.1–70.9] *vs.* 62.8% [95 CI 50.7–74.9]; log-rank test p = 0.970) groups (Fig. 3C).

4. Discussion

Testing for HER2 in invasive breast cancer is recommended by all international guidelines because of its significant impact on prognosis and treatment. Until recently, only HER2-positivity (as 3+ or 2+/ISH+) versus HER2-negativity (as 0, 1+ or 2+/ISH−) was of interest. The recent results of clinical trials evaluating anti-HER2 ADCs in HER2-low metastatic BC shifted this HER2 paradigm with the emergence of HER2-low tumours (1+ or 2+/ISH−) as a new relevant subtype [9,11]. Data suggesting HER2-low BC as a distinct disease entity with intrinsic characteristics have been reported [2,3,13]. However, the relevance of this IHC/ISH subtype is not clear, and a better understanding of the clinical behaviour and prognosis of HER2-low BC is lacking. In this retrospective analysis based on the database of our Organization European Cancer Institute-accredited comprehensive cancer center, we observed that HER2-low was associated with HR-positivity in a large series of 1111 early BC patients. The pCR rates were not impacted by HER2-status

Table 3
Associations of clinicopathological variables and pCR in multivariate binary logistic regression analysis.

		Odd ratio [CI 95%]			*p-value*
HER2 status	HER2-0 (0+)	Reference category			
	HER2-low (1+ 2+)	0.91	0.67	1.24	0.559
Age, years	≤40	Reference category			
	41–49	0.90	0.59	1.35	0.598
	50–74	0.59	0.41	0.86	0.005
	≥75	0.43	0.18	1.03	0.059
Hormone receptor (HR) status	HR-negative	Reference category			
	HR-positive	0.32	0.23	0.44	<0.001
cT stage	cT0-1	Reference category			
	cT2	1.00	0.66	1.52	0.995
	cT3	0.56	0.33	0.95	0.032
	cT4	0.83	0.37	1.85	0.645
Grade	1	Reference category			
	2	2.51	0.75	8.40	0.135
	3	6.19	1.86	20.55	0.003
cN stage	cN0	Reference category			
	cN ≥ 1	0.72	0.53	0.99	0.043
	Unknown	0.90	0.26	3.13	0.867
Surgery	Conservative	Reference category			
	Mastectomy	1.03	0.75	1.42	0.844

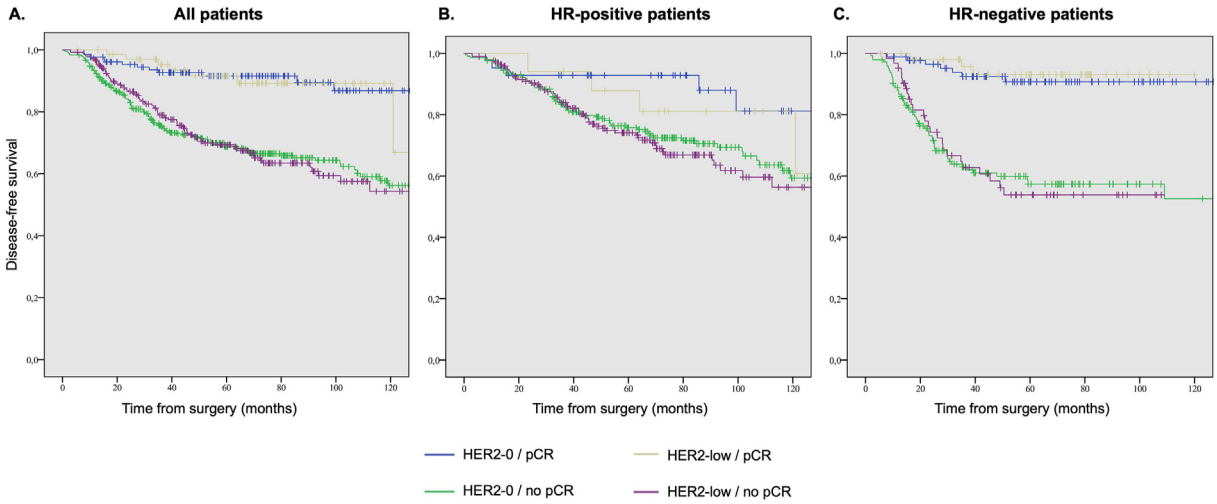

Fig. 3. Kaplan–Meier survival analysis for DFS in all, HR-positive, and HR-negative patients.

(HER2-low *vs.* HER2-0) in the whole cohort, nor in the HR-negative subgroup. However, when considering HR-positive patients, in which pCR rates are known to be low, HER2-low was associated with lower levels of pCR than HER2-0. HER2-status did not impact DFS, independently of HR expression.

Previous published studies reported pCR rates in HER2-low BC patients treated with chemotherapy [4,8,14–17] (Supplementary Fig. 3). In a pooled analysis of four neoadjuvant trials of the German Breast Group (N = 2310 patients), Denkert *et al.* reported similar associations between HR-positivity and HER2-low status (64% of HR-positive tumours, compared to 63% in our study). Similarly to our results, HER2-low tumours had a significantly lower pCR rate than HER2-0 tumours in univariate analysis (29.2% *vs.* 39.0%, compared to 23% *vs.* 30% in our study), but the statistical significance was also lost in multivariate analysis. Yet, there was a significant interaction between HER2 and HR-status, the pCR being consistently lower in HER2-low versus HER2-0 tumours, but only in the HR-positive subgroup. In a single center study including 855 patients, de Moura Leite *et al.* reported a similar trend for pCR in HR-negative patients (51%% pCR in HER2-low *vs.* 47% in HER2-0), that was inverted for HR-positive patients (13% pCR in HER2-low *vs*. 9.5% in HER2-0; p = 0.27) [14]. Very similar results were observed by Miglietta *et al.* in a 261 patients' cohort (Supplementary Fig. 3) [15]. Trends in pCR reported by two other groups [16,17] in HR-negative patients showed higher numerical value for HER2-0 tumours (Supplementary Fig. 3). More recently, Tarantino *et al.* described the outcomes of 657 patients receiving neoadjuvant chemotherapy [8]. Those with HER2-0 tumours had higher pCR rates compared with HER2-low (27% *vs.* 17%). However, the statistical difference was lost when separately analysing patients with HR-positive (but with a similar trend as observed in our study: 8% in HER2-low *vs.* 14 in HER2-0%, p = 0.08; or HR-negative (30.8% *vs.* 35.4%) tumours, and when adjusting for confounders). Thus, most of these studies showed no statistical difference when accounting for HR expression with pCR rates results that seems close from each other. Denkert *et al.* study, as the present one, show a slight negative impact of HER2-low on pCR rates when compared to HER2-0, although the association of higher pCR with HER2-0 was maintained in multivariate analysis in our series only. While the reasons for these discordances are unclear, they may rely upon differences in pathological evaluation of HER2-low status, statistical analyses, sample size or other unknown confounding variables, including our HR+ and TNBC tumours subdivision by using a 10% cut-off for HR expression. Expression percentages for oestrogen and progesterone receptors were available for 992 patients. When considering a 1% cut-off, 24 "HR-negative" patients by using the 10% cut-off would be reallocated to the "HR-positive" group. This reallocation did not modified the trends we observed in our results (pCR in HER2-0 *vs.* HER2-low tumours in all patients: 27% *vs.* 21% (p = 0.024), in HR-positive BC: 17% versus 12% (p = 0.095), and in HR-negative BC: 38% versus 42% (p = 0.508)). Nevertheless, these results suggest that HER2-low status may negatively impact the probability of reaching pCR in luminal BC, a subtype with classical resistance to conventional cytotoxics, and thus provide additional support to test ADCs anti-HER2 in HER2-low, HR-positive BC treated in the neoadjuvant setting. The pCR rates in HER2-low tumours reported in the present study and others will provide precious references for the standard arm in the future clinical trials of NACT incorporating these drugs: between 17% and 29% in the whole population, between 8% and 17.5% in the HR-positive tumours, and between 31% and 46% in the HR-negative tumours.

Regarding survival, our patients with HER2-0 and HER2-low tumours had similar 3-year DFS in the whole population with and without stratification upon

the pCR status. In the literature, conflictual data exist about the prognostic significance of HER2-low in early BC. In their analysis [4], Denkert *et al.* found longer DFS and OS in the HER2-low patients than HER2-0 patients in the whole population and in the HR-negative patients: these differences remained significant in multivariate analyses, suggesting independent prognostic value. For example, the patients with HER-low tumours displayed 83.4% 3-year DFS (95 CI 80.5–85.9) versus 76.1% (72.9–79.0) in patients with HER2-0 tumours ($p = 0.0084$), and 91.6% 3-year OS (84.9–93.4) *vs.* 85.8% (83.0–88.1), respectively ($p = 0.0016$). According to HR status, differences existed in HR-negative patients with no pCR (3-year DFS of 79% [95 CI 71.3–84.8] for HER2-low *vs.* 63.4% [57.4–68.8] for HER2-0). No difference by HER2 status was seen in patients with HR-positive tumours regardless of pCR status, nor in patients with HR-negative and pCR. In all the other studies, including ours [8,14–17], no difference in DFS or overall survival depending on HER2-low expression was observed. Other studies reported either no influence on the risk of recurrence or death [5,6], or worse prognosis for HER2 IHC 2+ tumours [7], or better prognosis for HER2-low tumours [18]. In the metastatic setting, HER2-low does not seem to impact survival outcomes [2], as we recently reported in HR-negative patients in a multicentric European cohort [19], although a recent Chinese study reported better OS in HR-negative patients [20].

Despite careful methodology aimed at minimising bias, our study has some limitations, lying mainly in its retrospective design. The HER2 status was extracted from the available pathology reports, and inter-pathologist variability in the differentiation of HER2-0 and HER2-low (1+), could have influenced our results [21]. Additionally, HER2 status was only considered on biopsy specimen before neoadjuvant treatment. An overall rate of HER2 expression discordance of 26.4% was recently reported, mostly driven by HER2-negative cases converting either from (14.8%) or to (8.9%) HER2-low-positive phenotype [15]. Another potential confounder is the fact that HER2-testing was performed in a timeframe over 15 years in which the standards of staining techniques and the guidelines for interpretation have slightly changed [1]. Nevertheless, tumour features were analysed by highly trained national BC expert pathologists with standardised procedures for HER2 testing and reporting, which should minimise this potential bias.

5. Conclusion

To the best of our knowledge, the present series is the largest real-life series assessing the pathological response to neoadjuvant chemotherapy in HER-0 *vs.* HER2-low patients. We showed that HER2-low status was associated with HR-positivity and that lower pCR rates were observed in HER2-low HR-positive patients, but not in HR-negative ones. This observation might support the development of anti-HER2-low therapeutic agents in the neoadjuvant treatment of HER2-low HR-positive patients to achieve better pCR. Information about the pCR rate after standard neoadjuvant chemotherapy in this population will be useful to design the future clinical trials testing new drugs such as anti-HER2 ADCs in this setting. HER2-low status did not impact DFS in our cohort.

Ethics approval

This cohort study was approved by our institutional review board (Registered study in Clinical research Department of Paoli-Calmettes Institute: IPC 2022-019 – date of approval: 29/06/22). All procedures performed in this study involving human participants were done in accordance with the French ethical standards and with the 2008 Helsinki Declaration.

Author contributions

Alexandre de Nonneville: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the article.

Gilles Houvenaeghel: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the article.

Monique Cohen: Collected the data, Wrote the article.

Laura Sabiani: Collected the data, Wrote the article.

Marie Bannier: Collected the data, Wrote the article.

Frederic Viret: Collected the data, Wrote the article.

Anthony Gonçalves: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Wrote the article.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alexandre de Nonneville declares the following competing interest: Gilead (lecture fees, congress invitation), Seagen (consulting fees), Daiichi Sankyo (congress invitation). Frederic Viret

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.09.017.

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