

Dose-dense adjuvant chemotherapy in HER2-low breast cancer: An exploratory analysis of the GIM2 trial

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ABSTRACT

Background: Dose-dense (DD) adjuvant chemotherapy represents a standard treatment for patients with high-risk node-positive early-stage HER2-negative breast cancer (BC). In this exploratory analysis of the GIM2 trial, we investigated the efficacy of DD chemotherapy among patients with HER2-negative BC according to HER2 immunohistochemistry (IHC) score.

Methods: Patients with node-positive early BC were randomized to receive either DD or standard schedule anthracycline- and taxane-based chemotherapy. HER2 status was assessed locally. Tumours with HER2 score 0 were classified as HER2-zero, those with a HER2 score 1+ or 2+ without ISH amplification as HER2-low. Tumours classified as HER2-negative with unknown IHC score were considered as a separate subgroup.

Results: Overall, 1243 subjects were eligible for this analysis, with 475 (38.2%) tumours classified as HER2-zero, 446 (35.9%) as HER2-low and 322 (25.9%) as HER2-negative with unknown IHC score. At a median follow-up of 14.9 years (IQR 8.4-16.2), no interaction was observed between treatment effect and HER2 status in invasive disease-free survival (iDFS) (p for interaction = 0.42) nor in overall survival (OS) (p for interaction = 0.34). Efficacy of DD chemotherapy was observed regardless of HER2 status: among patients with HER2-zero tumours, adjusted hazard ratio (aHR) for iDFS was 0.62 (95% confidence interval [CI] 0.45-0.85) and for OS was 0.55 (95% CI 0.36-0.84). Among patients with HER2-low tumours, aHR was 0.82 (95% CI 0.61-1.11) for iDFS and 0.84 (95% CI 0.57-1.23) for OS.

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Conclusions: In patients with HER2-negative high-risk early BC, the benefit of DD chemotherapy was observed irrespective of HER2 status. (NCT00433420)

1. Introduction

The HER2-low status, defined as a immunohistochemistry (IHC) score for HER2 of 1+ or 2+ without ISH amplification, has emerged in the last years as a therapeutic target after the development of the antibody-drug conjugate (ADC) Trastuzumab Deruxtecan, and the results of DESTINY-Breast 04 and 06 trials [1–3]. In parallel with these advances, interest has grown in understanding whether HER2-low breast cancers also differ in their sensitivity to conventional treatments. [4]. A comprehensive meta-analysis demonstrated that patients with HER2-low breast cancer have a lower rate of pathologic complete response (pCR) but better overall survival (OS) compared to those with HER2-zero tumours. The authors concluded that the prognostic differences between subjects affected by HER2-low and HER2-zero breast cancer are mainly driven by the hormone receptor status [5]. In fact, HER2-low breast cancers are more likely to be hormone receptor–positive and, consequently, less sensitive to chemotherapy, while exhibiting better long-term survival outcomes [5,6]. Given that approximately half of all breast cancers are ultimately classified as HER2-low [6], clarifying whether their response to chemotherapy differs from HER2-zero tumours is clinically relevant. Moreover, this could be particularly important when planning future clinical trials in the early setting.

Sequential anthracycline- and taxane-based chemotherapy represents the standard of care in the adjuvant setting, resulting in a reduction in mortality of about 30% [7]. The GIM2 phase III trial enrolled 2091 patients with node-positive early breast cancer and established the efficacy of dose-dense (DD) anthracycline- and taxane-based chemotherapy. At a median follow-up of 15.1 years, patients assigned to the DD arm had a significantly better disease-free survival (DFS) and OS compared to those enrolled in the standard-interval (SI) arm [8].

On the contrary, there was no apparent benefit of DD chemotherapy in patients with HER2-positive disease who received trastuzumab [9]. Consistently, no statistically significant differences in terms of survival outcomes were observed in the HE10/05 Trial, in which patients with HER2-positive breast cancer were randomized to receive either standard interval or DD chemotherapy, with both regimens followed by trastuzumab [10]. Similar findings were reported in the PANTHER trial [11]. Based on these results, the use of DD chemotherapy is debated in patients with HER2-positive breast cancer [9].

To date, no data are available about the efficacy of DD chemotherapy in patients affected by HER2-low breast cancer. In this exploratory analysis of the GIM2 trial, we therefore investigated the efficacy of DD chemotherapy among patients affected by HER2-negative breast cancer according to HER2 IHC score (low vs. zero).

2. Methods

2.1. Study design and participants

The design of the GIM2 study was previously described [8]. In summary, GIM2 was a 2 × 2 factorial, randomized, open-label, phase 3 trial, aiming to evaluate both the addition of fluorouracil to anthracycline and taxane, and the DD schedule in the adjuvant chemotherapy of patients with node-positive early breast cancer. The main inclusion criteria were diagnosis of early breast cancer with at least one axillary positive lymph node and no radiological evidence of distant metastases. Enrolled patients were randomized with a 1:1:1:1 ratio to one of the following arms: four cycles of standard interval epirubicin 90 mg/m², cyclophosphamide 600 mg/m², on day 1, every 3 weeks followed by

four cycles of paclitaxel 175 mg/m² on day 1, every 3 weeks (EC-P); four cycles of standard interval fluorouracil 600 mg/m², epirubicin 90 mg/m², cyclophosphamide 600 mg/m², on day 1, every 3 weeks) followed by four cycles of intravenous paclitaxel 175 mg/m² on day 1, every 3 weeks (FEC-P); DD EC-P every 2 weeks; and DD FEC-P every 2 weeks. Hormone receptor status was assessed locally in every institution participating in the trial and defined as positive in the case of at least 10% of positive cells by immunohistochemical analysis. HER2-positivity was defined locally by the presence of at least 10% of tumour cells with HER2 protein expression assessed by IHC or in-situ hybridization assay. A 2+ score was given in the case of weak to moderate complete membrane staining in more than 10% of tumour cells, necessitating ISH analysis (amplified or not amplified). HER2 1+ score was defined by incomplete, faint, or barely perceptible membrane staining in more than 10% of cancer cells. HER2-zero score was determined by either no staining or incomplete and faint membrane staining in less than 10% of cancer cell. The study was approved by ethics committees of all participating institutions. Written, informed consent was signed by all patients before study entry. This trial is registered in [ClinicalTrials.gov](https://clinicaltrials.gov), NCT00433420.

2.2. Outcomes

This is an exploratory analysis of the GIM2 trial aiming to evaluate the efficacy of DD chemotherapy among patients affected by HER2-negative breast cancer according to HER2 IHC.

HER2-zero breast cancers were defined as those with a score of 0 at IHC, while HER2-low breast cancers were classified as those with an IHC score of 1+ or 2+ without ISH amplification. Some tumours were defined as HER2-negative with unknown IHC score and considered as a separate subgroup.

Considering the lack of benefit with the addition of fluorouracil to EC-P regimen [8], the present analysis was conducted to estimate the efficacy of DD chemotherapy in HER2-low breast cancer regardless of fluorouracil administration.

2.3. Statistical analysis

Descriptive statistics were used to summarize continuous and categorical variables according to HER2 status. Continuous variables were reported as medians and interquartile ranges (IQRs), while categorical variables as frequencies and percentages. Invasive DFS (iDFS) and OS were defined as primary and secondary endpoints as per STEEP criteria [12]. iDFS was calculated from the date of randomization to the date of local recurrence, distant metastases, contralateral or ipsilateral breast tumour (excluding ductal carcinoma in situ), second primary malignancy, or death from any cause, whichever came first. This definition is identical to the definition used in the primary GIM2 publication, and was retained to ensure full consistency with the original trial design. OS was calculated from the date of randomization to the date of death from any cause. iDFS and OS of patients without an event were censored on the day of the last contact.

Survival estimates were computed through the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariable Cox proportional hazard models were used to estimate the association of HER2 status with survival outcomes. Multivariable models included, beyond HER2 classification, variables with known prognostic implications (i.e. treatment, age, type of surgery, histology, tumour size, nodal status, grade and hormone receptor status). The efficacy of DD chemotherapy according to HER2 status was evaluate using survival models

including the interaction term between HER2 status and DD chemotherapy. Median follow-up time was estimated through the reverse Kaplan-Meier method. All reported P values are two-sided, and $p < 0.05$ was considered statistically significant. The present analysis was not pre-planned in the protocol and therefore it must be considered exploratory. No adjustment for multiple testing was performed. All statistical analyses were performed using SAS version 9.4.

3. Results

3.1. Patients selection and baseline characteristics

Among 2091 patients enrolled in the GIM2 trial, 452 were excluded from the present analysis due to HER2-positivity, 88 due to enrolment in centres providing only SI chemotherapy, and 308 due to unknown HER2 status, leaving 1243 (59.4%) eligible subjects (Fig. 1). Median age was 52 years (IQR 44–59). A total of 475 (38.2%) tumours were classified as HER2-zero, 446 (35.9%) HER2-low, and 322 (25.9%) were HER2-negative with unknown IHC score. Baseline characteristics of patients in these three subgroups are reported in Table 1.

Similar percentage of ductal invasive carcinoma (around 79%) and of lobular invasive carcinoma were observed among patients with HER2-zero and HER2-low tumours (approximately 14%).

T2 tumours were slightly less frequent in patients with HER2-zero breast cancers, compared to those with HER2-low and HER2-negative tumours (36.6% vs. 43.7% vs. 39.8%, respectively).

Hormone receptor status was positive in around 87% of all three subgroups. A high rate of Ki67 ($>20\%$) was found in 43.4% ($N = 206$) of HER2-zero cancers, 57.4% ($N = 256$) of HER2-low cancer and 36.7% ($N = 118$) of those with unknown IHC score.

Grade 3 tumours were 38.3% ($N = 182$) in the HER2-zero group, 45.3% ($N = 202$) in the HER2-low group, 36.7% ($N = 118$) in the HER2-negative group with unknown IHC score.

3.2. Survival outcomes of HER2-low breast cancer versus HER2-zero breast cancer

At a median follow-up of 14.9 years (IQR 8.4–16.2), a total of 460 iDFS events were documented: 41 (8.9%) loco-regional recurrences, 257 (55.8%) distant relapses, 11 (2.4%) concurrent distant and regional recurrences, 44 (9.6%) new primary breast cancers, 45 (9.8%) second primary non-breast malignancies, and 58 (12.6%) deaths without prior relapse. In addition, 4 cases (0.8%) relapsed with an unknown site. The distribution of second primary malignancies and deaths without recurrence was comparable between the HER2-zero and HER2-low groups (Table 2). Comparing patients with HER2-low breast cancer to those affected by HER2-zero tumours, no significant differences in iDFS were observed (15yr iDFS rates were 54% vs. 61%, respectively, adjusted hazard ratio (aHR) 1.13, 95% confidence interval [CI] 0.91–1.40, $p = 0.48$) (Fig. 2). Similarly, no differences in OS were reported (15yr OS rates were 72% vs. 75%, aHR 1.10, 95% CI 0.83–1.46, $p = 0.46$) (Fig. 3). As regards the patients affected by HER2-negative breast cancer with unknown IHC score, the 15yr-iDFS was 55% and 15yr OS was 67%. Further details on hazard ratios, including both unadjusted and adjusted estimates, are provided in Supplementary Materials (Tables S1, S2, S3, S4).

3.3. Dose-dense efficacy according to HER2 status

No significant interaction was observed between treatment effect and HER2 status in iDFS (p for interaction = 0.42) or in OS (p for interaction = 0.34). When investigating DD schedule efficacy among patients with HER2-zero tumours, aHR for iDFS was 0.62 (95% CI 0.45–0.85) with 15yr iDFS rates at 53% for the SI arm, and 69% for patients treated with DD regimen (Fig. 4A). aHR for OS was 0.55 (95% CI 0.36–0.84), with 15yr OS rate of 70% for the SI arm and 81% for the DD arm (Fig. 5A). Within patients affected by HER2-low breast cancer, aHR was 0.82 (95% CI 0.61–1.11) for iDFS (Fig. 4B). 15yr iDFS rate was 57% for patients treated with DD chemotherapy and 50% for those treated with standard interval schedule. 15yr OS in this subgroup of patients was 70% in those treated with standard interval regimen and 73% in subjects

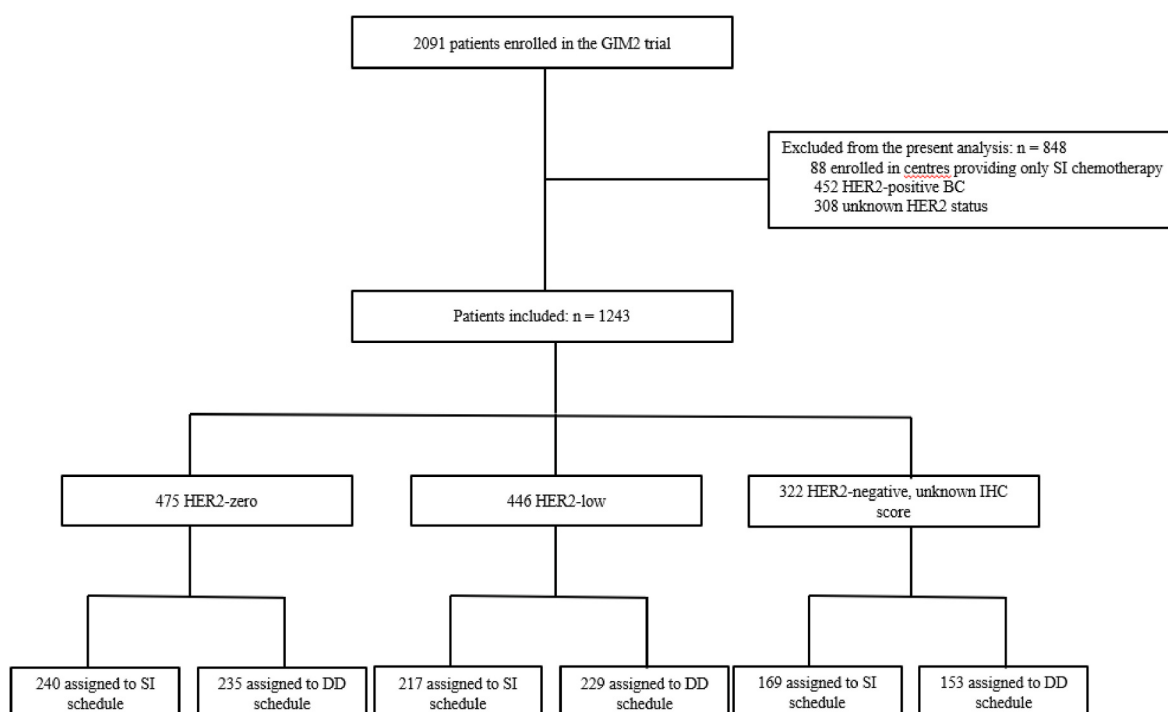


Fig. 1. CONSORT diagram. BC, breast cancer; DD, dose-dense; SI, standard interval.

Table 1
Baseline characteristics.

	HER2-zero, N = 475 (%)	HER2-low, N = 446 (%)	HER2-negative with unknown IHC score, N = 322 (%)	p-value
Treatment arm				NA
Standard-interval	240 (50.5)	217 (48.6)	169 (52.5)	
Dose-dense	235 (47.5)	229 (51.4)	153 (47.5)	
Menopausal status				0.157
Pre-menopausal	235 (49.5)	227 (50.9)	142 (44.1)	
Post-menopausal	240 (50.5)	219 (49.1)	180 (55.9)	
Surgery				0.787
Mastectomy	176 (37.1)	168 (37.7)	127 (39.4)	
Lumpectomy	299 (62.9)	278 (62.3)	195 (60.6)	
Histologic type				0.943
Ductal	375 (79.0)	356 (79.8)	254 (78.9)	
Lobular	68 (14.3)	64 (14.4)	50 (15.5)	
Other	32 (6.7)	26 (5.8)	18 (5.6)	
Tumour Size				0.482
T1	263 (55.4)	227 (50.9)	171 (53.1)	
T2	174 (36.6)	195 (43.7)	128 (39.8)	
T3	21 (4.4)	14 (3.1)	12 (3.7)	
T4	16 (3.4)	9 (2.0)	9 (2.8)	
Unknown	1 (0.2)	1 (0.2)	2 (0.6)	
Nodal Status				0.714
N1	297 (62.5)	274 (61.4)	204 (63.3)	
N2	110 (23.2)	112 (25.1)	82 (25.5)	
N3	68 (14.3)	60 (13.5)	36 (11.2)	
Grading				0.006
G1	47 (9.9)	19 (4.3)	19 (5.9)	
G2	233 (49.1)	217 (48.7)	176 (54.7)	
G3	182 (38.3)	202 (45.3)	118 (36.7)	
Unknown	13 (2.7)	8 (1.8)	9 (2.8)	
Hormone receptor status				0.279
Negative	64 (13.5)	46 (10.3)	40 (12.4)	
Positive	411 (86.5)	400 (89.7)	281 (87.3)	
Unknown	0 (0)	0 (0)	1 (0.3)	
Ki67 value				<0.001
0-14	167 (35.2)	107 (24.0)	107 (33.2)	
15-20	49 (10.3)	35 (7.9)	34 (10.6)	
>20	206 (43.4)	256 (57.4)	118 (36.6)	
Unknown	53 (11.1)	48 (10.7)	63 (19.6)	

Table 2
Invasive Disease-Free Survival (iDFS) events.

Type of iDFS events	HER2-zero N = 160 (%)	HER2-low N = 179 (%)	HER2-negative with unknown IHC score, N = 121 (%)	Total
Locoregional alone	15 (9.4%)	16 (8.9%)	10 (8.3%)	41 (8.9%)
Distant	91 (56.9%)	109 (60.9%)	57 (47.1%)	257 (55.9%)
Concurrent locoregional and distant	7 (4.4%)	1 (0.6%)	3 (2.5%)	11 (2.4%)
Unknown site	2 (1.2%)	2 (1.1%)	0 (0.0%)	4 (0.9%)
Primary breast cancer	13 (8.1%)	19 (10.6%)	12 (9.9%)	44 (9.6%)
Second primary non-breast	16 (10.0%)	19 (10.6%)	10 (8.3%)	45 (9.8%)
Death without relapse	16 (10.0%)	13 (7.3%)	29 (24.0%)	58 (12.6%)

treated with DD schedule (aHR 0.84, 95% CI 0.57-1.23) (Fig. 5B). The subpopulation with HER2-negative breast cancer with unknown IHC score exhibited a 15yr iDFS of 53% in the SI arm and 58% in the DD arm (Fig. 4C), and a 15yr OS rate of 63% and 71%, respectively (Fig. 5C).

4. Discussion

In the present analysis of the GIM2 trial, we showed that DD chemotherapy is effective in patients with HER2-negative breast cancer, regardless of HER2 status (low vs. zero). At a median follow-up of about 15 years, the absolute difference between the DD schedule arm and the SI arm was approximately 16% in terms of iDFS rate in patients with HER2-zero breast cancer, and 10% in terms of OS, while among subjects with HER2-low tumours the differences were 7% and 3%, respectively, with no significant interaction between treatment arm and HER2 status. Taken together, these findings support the use of DD chemotherapy in node-positive breast cancer independently of HER2 expression level (zero or low), as this approach consistently improves long-term outcomes.

These results should be interpreted in the context of the established role of DD chemotherapy in early breast cancer, which represents the standard-of-care treatment for high-risk early breast cancer, with a demonstrated reduction in breast cancer mortality exceeding 30% [7]. The EBCTCG meta-analysis confirmed that shortening the interval between anthracycline cycles improves long-term outcomes, independently of hormone receptor status, thereby supporting the broad applicability of DD strategies [7,13]. Similarly, long-term results from the MIG-1 trial showed a persistent, although modest, benefit of DD FEC compared with the SI schedule. In this case, the benefit was stronger in those with hormone receptor-negative tumours [14]. However, none of these studies evaluated whether the magnitude of benefit associated with DD chemotherapy varies according to HER2 expression.

Evidence regarding HER2-positive disease is also limited. In an exploratory analysis of the GIM2 trial, Lambertini et al. assessed the effect of DD chemotherapy in patients with HER2-positive breast cancer, showing no apparent benefit among those treated with trastuzumab. [9]. Additional insights come from the PANTHER trial, which included a secondary analysis comparing outcomes between HER2-positive and HER2-negative patients treated with tailored DD versus SI chemotherapy. This analysis suggested a nonsignificant trend toward improved relapse-free survival with the DD approach in HER2-positive disease [11]. Despite being restricted to HER2-positive cohorts, these data point to a persistent uncertainty regarding the extent to which HER2 expression levels may modulate the efficacy of DD chemotherapy. In this context, our study provides novel evidence by demonstrating that the advantage of DD chemotherapy is maintained irrespective of HER2 expression level in patients with HER2-negative tumours.

HER2-low status represents a therapeutic target for ADCs, particularly trastuzumab deruxtecan. The DESTINY-Breast 04 and 06 trials showed the efficacy of trastuzumab deruxtecan in reducing the risk of progression in patients with metastatic HER2-low breast cancer [2,3].

Although the prognostic value of the HER2-low status has been largely debated, a comprehensive meta-analysis including more than one million patients, showed that, while small prognostic differences exist between subjects with HER2-zero and HER2-low breast cancer, survival outcomes are primarily driven by hormone-receptor status [5]. This concept is further reinforced by the ESMO consensus on HER2-low breast neoplasms, which also emphasizes the relevance of intrinsic tumour biology [15]. Our findings are consistent with this evidence. Although the DD schedule appears more effective than SI administration in both HER2-low and HER2-zero tumours, the absolute difference in iDFS rate and OS rate seems to be greater in those with HER2-zero tumours than in those with HER2-low cancers.

This pattern may reflect the distinct biological landscape of HER2-low cancers, which show a higher prevalence of luminal intrinsic subtypes, as demonstrated by Schettini et al., who reported that HER2-low tumours are predominantly luminal by PAM50 [6]. While PAM50 analysis was not available in our cohort, the slightly higher proportion of hormone-receptor-positive tumours in the HER2-low group compared with the HER2-zero subgroup (89.7% vs. 86.5%) might support this interpretation. In line with these biological features, patients with

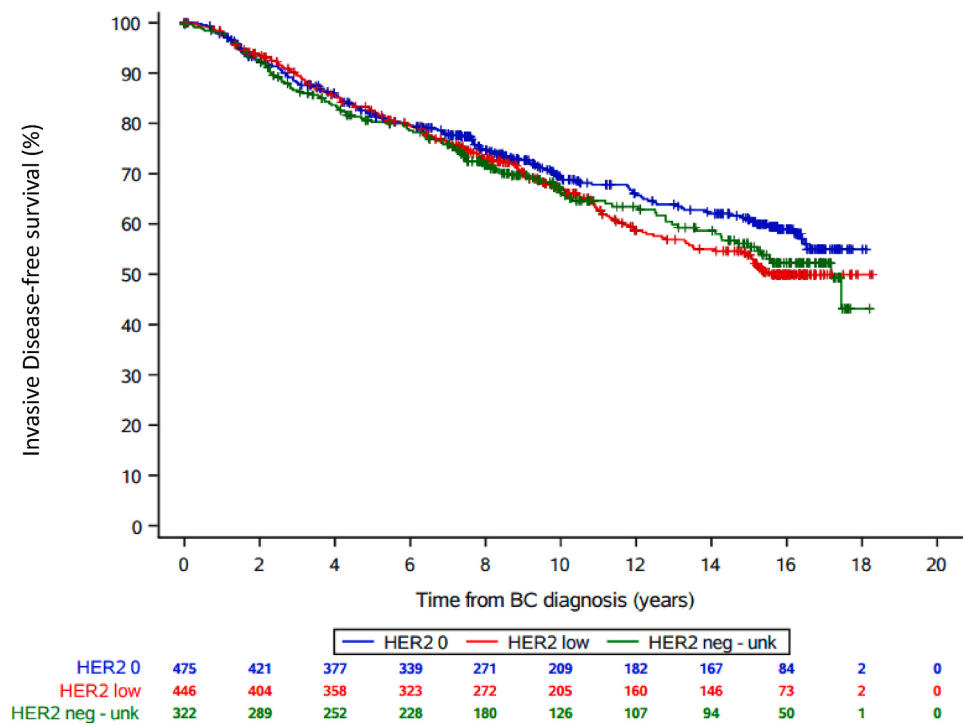


Fig. 2. Invasive Disease Free-Survival HER2 zero vs. HER2-low vs HER2-neg.

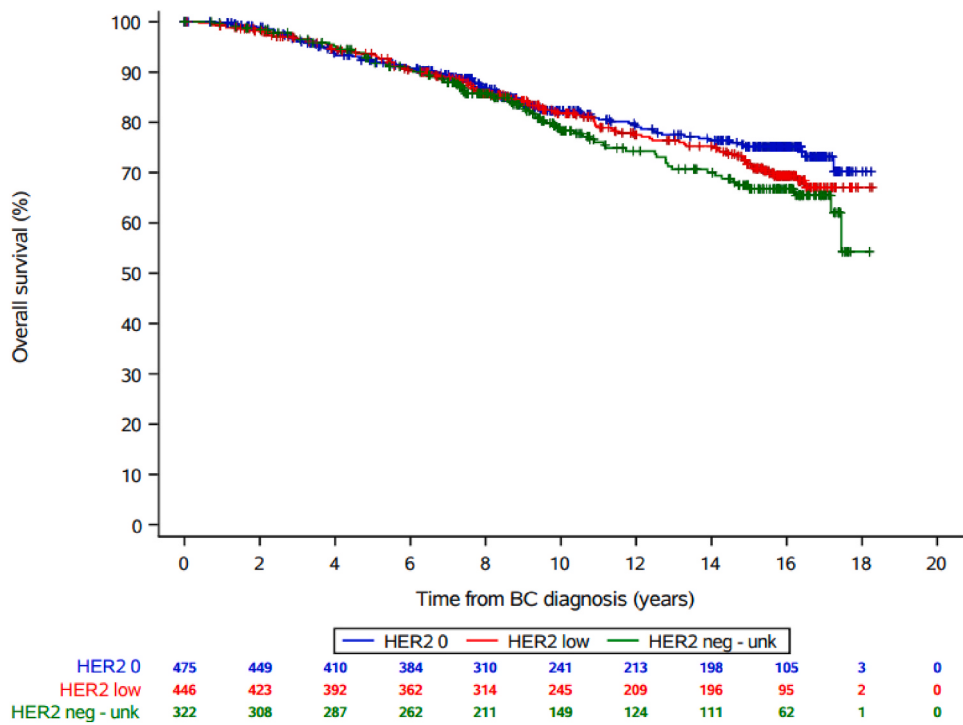


Fig. 3. Overall Survival HER2 zero vs. HER2-low vs HER2-neg.

HER2-low tumours have been shown to achieve lower pCR rates following neoadjuvant chemotherapy compared with those with HER2-zero disease [5,16–18].

Due to this peculiar behaviour, additional agents should be investigated in early setting to obtain better survival outcomes in this subgroup of patients.

This sub-analysis seems to be useful considering the evolving clinical significance of HER2-low concept in early setting and the need to design

future clinical trials tailored to this population. According to literature data, HER2-low breast cancer represents about a half of breast cancer diagnoses and every clinician should be aware about how to treat these subjects [19]. Several ongoing clinical trials are specifically exploring novel therapeutic strategies for early-stage HER2-low breast cancer, reflecting the rapid evolution of this entity. A phase II trial is assessing trastuzumab deruxtecan, alone or combined with endocrine therapy, as preoperative treatment for early-stage HR-positive/HER2-low tumours

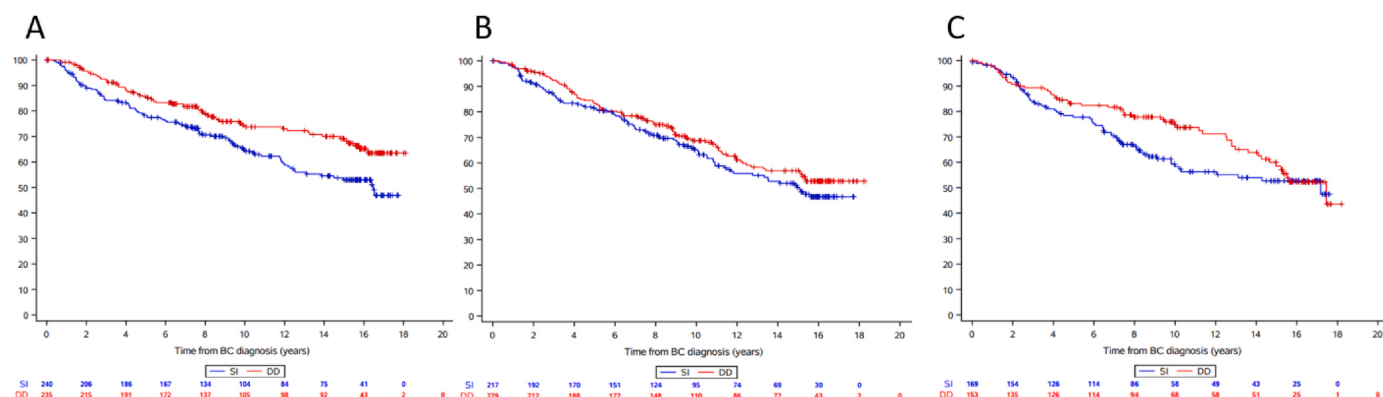


Fig. 4. Invasive disease-free survival in patients with HER2-zero breast cancer (panel A), HER2-low breast cancer (panel B) HER2-negative with unknown IHC score (panel C), according to dose-dense (DD) vs. standard interval (SI) administration.

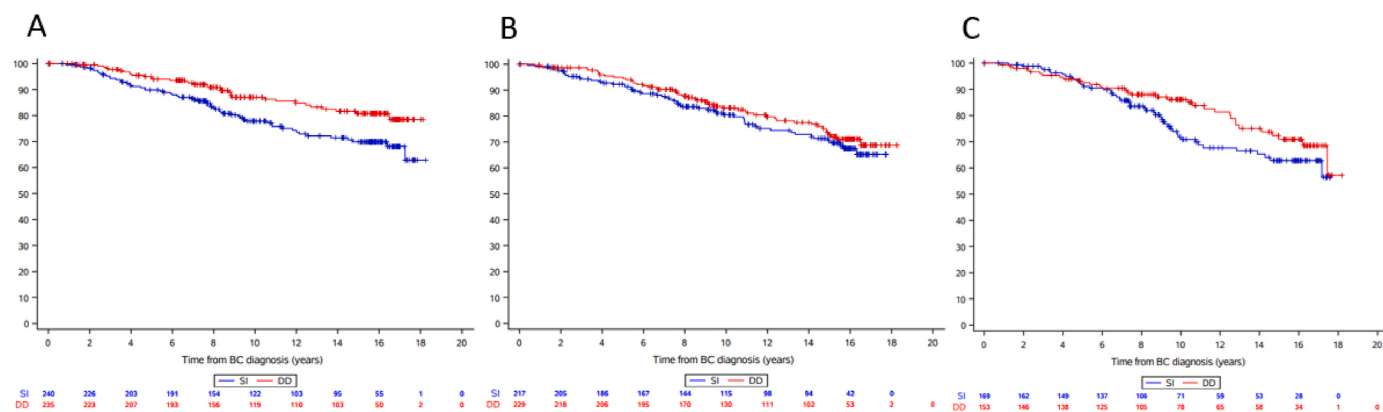


Fig. 5. Overall Survival in patients with HER2 zero breast cancer (panel A), HER2-low breast cancer (panel B) HER2-negative with unknown IHC score (panel C), according to dose-dense (DD) vs. standard interval (SI) administration.

(NCT04553770). Parallel efforts are investigating pyrotinib-based regimens, including randomized neoadjuvant trials combining pyrotinib with anthracycline–taxane chemotherapy in high-risk HR-positive/-HER2-low early breast cancer (NCT06144944) and single-arm studies pairing pyrotinib with EC followed by docetaxel (NCT05165225). In addition, several trials are testing the novel ADC SHR-A1811, either with chemotherapy and immunotherapy in the neoadjuvant setting (NCT07317778), or in randomized comparisons against standard chemotherapy with or without endocrine therapy (NCT07305246). Early-stage studies enrolling HR-low/HER2-negative populations—such as those evaluating patritumab deruxtecan or sacituzumab tirumotecan in combination with immunotherapy—also include dedicated HER2-low cohorts and may further inform treatment strategies. Collectively, these trials illustrate a growing interest in integrating biologically targeted approaches into the management of early HER2-low breast cancer, although none directly address the role of DD chemotherapy in this setting.

Our analysis has some limitations that must be considered: first, this is an unplanned, exploratory analysis. Second, no central revision of the tissue samples was performed to define the HER2 status. Nonetheless, to our knowledge, this is the first analysis evaluating DD efficacy in adjuvant setting specifically among patients affected by HER2-low breast cancer. The data are retrieved from the GIM2 trial, one of the most relevant studies establishing the efficacy of DD regimen in patients at high risk of recurrence.

In conclusion, this exploratory analysis of the GIM2 trial provides the first evidence that the benefit of DD chemotherapy is preserved across the full spectrum of HER2-negative disease, including both HER2-low

and HER2-zero tumours. Until prospective data clarify the role of biologically targeted approaches in the curative setting, our findings support DD chemotherapy as an effective and appropriate standard option for patients with node-positive HER2-negative breast cancer, irrespective of HER2 IHC score.

Data availability statement

The data that support the findings of this study are available on reasonable request to the Corresponding author, L.D.M.

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CRediT authorship contribution statement

Chiara Molinelli: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Virginia Delucchi:** Data curation, Formal analysis, Methodology, Software. **Eva Blondeaux:** Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Luca Boni:** Data curation, Writing – review & editing. **Francesca Poggio:** Data curation, Writing – review & editing. **Davide Soldato:** Data curation, Writing – review & editing. **Ludovica Antonj:** Data curation,

Writing – review & editing. **Grazia Arpino**: Data curation, Writing – review & editing. **Cecilia Nisticò**: Data curation, Writing – review & editing. **Alessandra Fabi**: Data curation, Writing – review & editing. **Michelino De Laurentiis**: Data curation, Writing – review & editing. **Giuseppe Buono**: Data curation, Writing – review & editing. **Fabio Puglisi**: Data curation, Writing – review & editing. **Guilherme Nader-Marta**: Conceptualization, Writing – review & editing. **Alessandra Fozza**: Data curation, Writing – review & editing. **Francesca Pitto**: Data curation, Writing – review & editing. **Federica Boncore**: Writing – review & editing. **Barbara Cardinali**: Writing – review & editing. **Piero Fregatti**: Writing – review & editing. **Matteo Lambertini**: Conceptualization, Data curation, Supervision, Validation, Writing – review & editing. **Lucia Del Mastro**: Conceptualization, Data curation, Formal analysis, Supervision, Validation, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CM reports consulting fees from Daiichi Sankyo, Medical Writing fees from Seagen, support for attending medical conferences from AstraZeneca and Menarini, Speaker honoraria from Accademia Nazionale di Medicina, all outside the submitted work. EB reports speaker fee from Eli Lilly and AstraZeneca and funding (to the institution) from Gilead Science. DS reported honoraria from Novartis, travel, accommodation, expensed from Novartis, Merck, Daiichi Sankyo. GA reported honoraria from Roche, Lilly, Novartis, Novartis (Inst), Pfizer, Pfizer (Inst), AstraZeneca; consulting or advisory Role from Roche, Eisai, Lilly, Pfizer, Novartis, Daiichi Sankyo/AstraZeneca, MSD Oncology; speakers' bureau from Roche, Pfizer, Lilly, Novartis, Helsinn Therapeutics/QED Therapeutics; research funding from Novartis (Inst), pfizer (Inst), eisai (Inst), Roche (Inst); travel, accommodations, expenses from Pfizer, Roche, Lilly, Daiichi Sankyo/AstraZeneca. MdL reported stock and other Ownership Interests from Arvinas; honoraria from Roche, Novartis, Pfizer, Lilly, Pierre Fabre, AstraZeneca, MSD, Seagen, Gilead Sciences, Ipsen, Exact Sciences, TOMA Biosciences, Daiichi Sankyo Europe GmbH, VeracYTE; consulting or Advisory Role from Roche, Novartis, Pfizer, Lilly, AstraZeneca, MSD, Pierre Fabre, Seagen, Gilead Sciences, Ipsen, Daiichi Sankyo Europe GmbH; speakers' bureau from Novartis Research Funding; Novartis (Inst), Roche (Inst), Lilly, Pfizer (Inst), Daiichi Sankyo (Inst), MSD (Inst), Bristol Myers Squibb (Inst), Genzyme (Inst), AstraZeneca (Inst). GB G. Buono reports consulting or Advisory Role from AstraZeneca, Daiichi Sankyo, Novartis, Genetic Spa, Wave Pharma; Speakers' Bureau: Novartis, Lilly, Pfizer, AstraZeneca, Daiichi Sankyo, Exact Sciences, Gilead, MSD, Pierre Fabre, Wave pharma, Genetic Spa; Research Funding to the Institution from: Gilead, AstraZeneca; Travel, Accommodations, Expenses from: Roche, Lilly, Novartis, Daiichi Sankyo, AstraZeneca, Gilead. FP reported honoraria for advisory boards, activities as a speaker, travel grants, research grants from Astrazeneca, Bayer, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, Ipsen, Italfarmaco, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen. Research funding from Astrazeneca, Eisai, Roche. FPo advisory board fees and/or honoraria from Eli Lilly, Novartis, AstraZeneca, Daiichi Sankyo, and Pfizer; meeting travel from Gilead, Novartis, Takeda. GNM reports honoraria from AstraZeneca. ML reports advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Gilead, MSD, Pierre Fabre, Menarini, Nordic Pharma, Bayer, Ipsen, Daiichi Sankyo; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, AstraZeneca, Takeda, Ipsen, Sandoz, Libbs, Daiichi Sankyo, Gilead, Menarini; receiving travel grants from Gilead, Roche, Daiichi Sankyo; receiving research funding (to his institution) from Gilead; having other financial interests as JCO Consultant Editor, Chair of the ESO Certificate of Competence in Breast Cancer, all outside the submitted work. LDM. reported grants from Eli Lilly, Novartis, Roche, Daiichi Sankyo, Seagen, AstraZeneca, Gilead, and Pierre Fabre; receiving consulting fees from Eli Lilly, Gilead, and Daiichi Sankyo; receiving speaker honoraria from Roche, Novartis, Pfizer, Eli

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Appendix A. Supplementary data

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