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ORIGINAL RESEARCH

HER2-Low Expression Predicts Improved Pathologic Response but not Disease-Free Survival in HR-Positive/HER2-Negative Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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ABSTRACT

This retrospective single-center study aims to evaluate the predictive and prognostic significance of HER2-low (IHC 1+/2+ ISH–) compared with HER2-0 status in hormone receptor (HR)-positive / HER2-negative breast cancer patients treated with neoadjuvant chemotherapy (NACT). A cohort of 404 HR-positive / HER2-negative breast cancer patients treated with NACT between January 2008 and December 2019 at Bursa Uludag University was analyzed. Clinicopathologic variables, pathologic complete response (pCR), and long-term survival were assessed. Logistic regression identified independent predictors of pCR, and Cox proportional hazards modelling was used for disease-free survival (DFS). Of 404 patients, 117 (29.0%) were HER2-low and 287 (71.0%) were HER2-0. The pCR rate was significantly higher in the HER2-low group than in the HER2-0 group (9.4% vs 4.2%; p = 0.040). Multivariable logistic regression analysis revealed that HER2-low status (OR=2.88; 95% CI, 1.17–7.12; p=0.022) and a higher Ki-67 index (OR =1.03 per 1% increase; 95% CI, 1.01–1.05; p=0.003) were independent predictors of pathological complete response (pCR). The median follow-up time was 110.2 months (range, 10.5–248.9 months). The 5- and 10-year DFS rates were 85.1% and 73.7%, respectively; OS rates were 86.4% and 75.3%. In multivariable Cox regression, only pathological stage remained an independent predictor of DFS (HR=2.02; 95% CI 1.55–2.61; p<0.001), while HER2 status was not significant (HR=0.97; 95% CI 0.66–1.43; p=0.861). In conclusion, HER2-low status was associated with improved pCR but not with long-term survival. Pathologic stage remained the strongest determinant of DFS, and HER2-low appears to represent a biologic continuum within HER2-negative disease rather than a distinct prognostic subtype.

Keywords: HER2-low breast cancer. Hormone receptor-positive breast cancer. Neoadjuvant chemotherapy. Pathologic complete response. Disease-free survival.

HER2-Düşük Ekspresyonunun, Neoadjuvan Kemoterapi Alan HR-Pozitif / HER2-Negatif Meme Kanseri Hastalarında Patolojik Yanıta ve Sağkalıma Etkisi

ÖZET

Bu çalışma, neoadjuvan kemoterapi (NAKT) uygulanan hormon reseptörü (HR) pozitif/HER2 negatif meme kanseri hastalarında HER2-0 durumu ile karşılaştırıldığında HER2-düşük (IHC 1+/2+ ve negatif ISH) durumunun öngörücü ve prognostik önemini değerlendirmeyi amaçlayan retrospektif tek merkezli bir çalışmadır. Ocak 2008 – Aralık 2019 tarihleri arasında Bursa Uludağ Üniversitesi'nde NAKT alan toplam 404 HR-pozitif / HER2-negatif hasta kohortu analiz edilmiştir. Klinikopatolojik değişkenler, pCR oranı ve uzun dönem sağkalım değerlendirilmiştir. Lojistik regresyon pCR'nin bağımsız belirleyicilerini, Cox regresyon modeli ise hastalıksız sağkalımı (DFS) değerlendirmek için kullanılmıştır. Hastaların %29,0'ı (n=117) HER2-düşük, %71,0'i (n=287) HER2-0 grubundaydı. pCR oranı HER2-düşük grupta anlamlı olarak daha yüksekti (%9,4'e karşı %4,2; p=0,040). Çok değişkenli analizde HER2-düşük durumu (OR=2,88; %95 GA: 1,17–7,12; p=0,022) ve yüksek Ki-67 indeksi (OR=1,03; %95 GA:1,01–1,05; p=0,003) pCR ile bağımsız olarak ilişkiliydi. Ortanca takip süresi 110,2 ay (10,5–248,9) idi. Beş ve on yıllık DFS oranları sırasıyla %85,1 ve %73,7; genel sağkalım (OS) oranları %86,4 ve %75,3 olarak bulundu. Çok değişkenli Cox analizinde yalnızca patolojik evre DFS için bağımsız belirleyici idi (HR=2,02; %95 GA: 1,55–2,61; p<0,001), HER2 durumu anlamlı bulunmadı (HR=0,97; %95 GA: 0,66–1,43; p=0,861). Sonuç olarak, HER2-düşük durumu artmış pCR oranı ile ilişkili olmasına rağmen uzun dönem sağkalım açısından avantaj sağlamamıştır. DFS'nin en güçlü belirleyicisi patolojik evre olarak kalmıştır. Bulgularımız, HER2-low hastalığın HER2-negatif spektrum içinde biyolojik bir sürekliliği temsil ettiğini ve ayrı bir prognostik alt tip olmadığını düşündürmektedir.

Anahtar Kelimeler: HER2-düşük meme kanseri. Hormon reseptör pozitif meme kanseri. Neoadjuvan kemoterapi. Patolojik tam yanıt. Hastalıksız sağkalım.

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Breast cancer is a biologically heterogeneous disease with distinct molecular subtypes that carry different prognostic and therapeutic implications[1]. Among these, the human epidermal growth factor receptor 2 (HER2) has traditionally been classified as either positive or negative, a dichotomy that guided treatment and prognosis for decades[2]. Recently, the concept of HER2-low breast cancer—defined as immunohistochemistry (IHC) 1+ or IHC 2+ with negative in situ hybridization (ISH)—has gained increasing attention[3].

HER2-low tumors represent an intermediate subgroup within the HER2-negative spectrum, characterized by low-level HER2 protein expression without gene amplification[4]. The advent of antibody–drug conjugates (ADCs), particularly trastuzumab deruxtecan (T-DXd), has expanded therapeutic options for this population, as demonstrated in the DESTINY-Breast04 trial, which showed significant survival benefits in patients with previously treated HER2-low metastatic breast cancer[5]. Beyond treatment implications, evidence suggests that HER2-low tumors may differ biologically and clinically from HER2-0 tumors regarding hormone receptor (HR) expression, proliferation, and differentiation patterns[6,7].

The majority of HER2-low tumors are HR-positive, yet the prognostic and predictive role of HER2 expression within this subset remains controversial[8]. While HR-positive cancers generally have lower pathologic complete response (pCR) rates to neoadjuvant chemotherapy (NACT) than triple-negative or HER2-positive disease[9], it remains uncertain whether HER2-low expression influences chemosensitivity or long-term survival. Some reports have demonstrated modestly improved pCR or disease-free survival (DFS) in HER2-low tumors[10-12], whereas others have found no significant differences in pCR or survival[13,14].

These conflicting data highlight ongoing debate over whether HER2-low disease represents a biologically distinct entity or merely reflects a continuum of HER2 expression[15]. Given these uncertainties, this study aimed to evaluate the relationship between HER2-low status and both pathologic complete response and survival outcomes in a large, single-center cohort of HR-positive / HER2-negative breast cancer patients treated with neoadjuvant chemotherapy. Given that the vast majority of HER2-low cases fall within the HR-positive category, restricting the current analysis to HR-positive / HER2-negative tumors allows for a more homogeneous cohort and minimizes potential confounding from the distinct biology and treatment response of triple-negative disease.

Material and Method

Study design and patient selection

This retrospective study was conducted at the Department of Medical Oncology, Bursa Uludag University Faculty of Medicine, Turkey. Female patients with histologically confirmed invasive breast cancer who received neoadjuvant chemotherapy (NACT) between January 2008 and December 2019 were screened, and 668 patients were identified from institutional oncology records.

Patients were excluded if they had missing clinicopathological data, a history of cardiac, hepatic, or renal failure, were younger than 18 years, had a previous malignancy, or had an unknown molecular subtype before initiating NACT. After applying these criteria, 668 patients with known molecular subtypes were included. Patients with HER2-positive (n=160) or triple-negative (n=104) disease were then excluded. The final study population consisted of 404 patients with hormone receptor (HR)-positive / HER2-negative breast cancer. The patient selection process is illustrated in Figure 1.

Clinicopathological assessment

Patient data were obtained from pathology reports in the majority of cases. In cases of clinicopathological discrepancy, histopathological re-evaluation was performed according to the ASCO/CAP guidelines (2018 update). Hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]) and HER2 status were determined by immunohistochemistry (IHC) on pretreatment

core biopsy specimens. Cases with IHC 3+ or IHC 2+ and positive fluorescence in situ hybridization (FISH) were considered HER2-positive. HER2-low was defined as IHC 1+ or IHC 2+ with negative FISH, while HER2-0 referred to the complete absence of membrane staining.

Histologic subtype and tumor grade were evaluated according to the WHO and modified Bloom–Richardson criteria. Clinical staging was based on the AJCC 8th edition TNM classification using baseline imaging.

Treatment protocol and response evaluation

All patients received standard neoadjuvant chemotherapy regimens without targeted therapy. After completion of chemotherapy, all patients underwent definitive surgery (either mastectomy or breast-conserving surgery) followed by radiotherapy and adjuvant endocrine treatment per standard institutional practice.

Pathologic complete response (pCR) was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/is ypN0). Pathologic response was evaluated by experienced breast pathologists.

Follow-up and survival analysis

Postoperative follow-up was conducted every 3-6 months during the first 2 years, every 6 months for years 3–5, and annually thereafter. Disease-free survival (DFS) was defined as the time from surgery to the first documented recurrence (local, regional, or distant) or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up.

Statistical analysis

Descriptive statistics were summarized as median (min-max) or mean ± standard deviation (SD) according to their distribution, and categorical variables were expressed as frequencies (%). Comparisons of categorical variables were performed using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's *t*-test or Mann–Whitney U test. Cases with missing clinicopathological or follow-up data were excluded from the corresponding analyses. Multivariate logistic regression analysis was performed, incorporating clinicopathologically significant variables to identify independent predictors of pathological complete response.

Survival analyses were performed using the Kaplan–Meier method, with differences compared by the log-rank test. Cox proportional hazards models were used for univariate and multivariate analyses of DFS. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

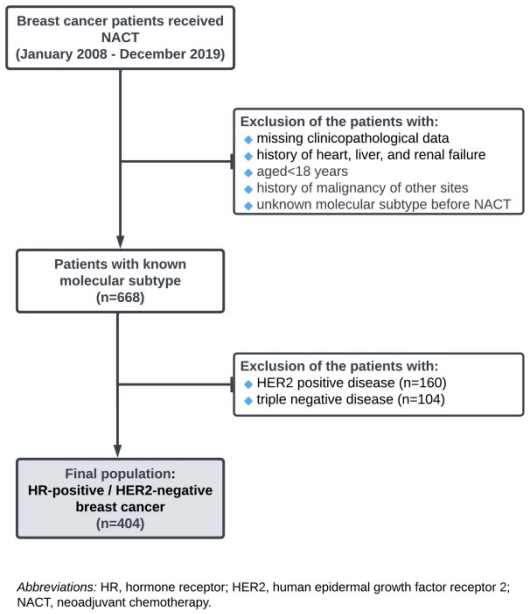
Ethical statement

This investigation adhered to the ethical principles of the Declaration of Helsinki and received authorization from the Bursa Uludag University Institutional Review Board (Approval ID: 2020-6/31).

Results

Patient characteristics

A total of 404 patients with hormone receptor (HR)–positive and HER2-negative breast cancer who received neoadjuvant chemotherapy (NACT) at Bursa Uludag University were included in the final analysis (Figure 1).



Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NACT, neoadjuvant chemotherapy.

Figure 1:
Flowchart of patient selection.

The median age at diagnosis was 47.5 years (range, 21.9–83.4). Among these patients, 210 (52.0%) were premenopausal. Most patients presented with T1–2 disease (74.5%), and clinical lymph node involvement was observed in 57.7%. The predominant histologic subtype was invasive ductal carcinoma (89.6%), and 10.4% had other histologies, including lobular or mixed types. The median Ki-67 index was 24% (range, 1–100).

Regarding treatment characteristics, 289 patients (71.5%) received an anthracycline plus taxane–

based NACT regimen, and 295 (73.2%) underwent breast-conserving surgery, while 108 (26.8%) had mastectomy. Overall, 23 patients (5.7%) achieved a pathologic complete response (pCR) in both breast and axilla, whereas 381 (94.3%) had residual invasive disease after NACT.

Based on pretreatment core biopsy, 287 patients (71.0%) were classified as HER2 IHC 0, and 117 (29.0%) as HER2 IHC 1+ or 2+ (HER2-low). The pCR rate was significantly higher in the HER2-low group compared with the IHC 0 group (9.4% vs 4.2%, p=0.040). Baseline clinicopathologic characteristics are summarized in Table I.

Table I. Baseline clinicopathologic characteristics of the study population

Variable	Total (n = 404)	IHC 0 (n = 287)	IHC 1+/2+ (n = 117)	p-value
Age, years, median (min-max)	47.5 (21.9-83.4)	47.5 (21.9-83.4)	47.8 (24.7-80.6)	0.24
Menopausal status				0.79
Premenopausal	210 (52.0%)	148 (51.6%)	62 (53.0%)	
Postmenopausal	194 (48.0%)	139 (48.4%)	55 (47.0%)	
Clinical T stage				0.17
cT1–2	292 (74.5%)	211 (76.4%)	81 (69.8%)	
cT3–4	100 (25.5%)	65 (23.6%)	35 (30.2%)	
Clinical N status				0.87
Negative	166 (42.3%)	118 (42.6%)	48 (41.7%)	
Positive	226 (57.7%)	159 (57.4%)	67 (58.3%)	
Histological subtype				0.13
Invasive ductal	362 (89.6%)	253 (88.2%)	109 (93.2%)	
Other	42 (10.4%)	34 (11.8%)	8 (6.8%)	
Ki-67, %, median (min-max)	24 (1–100)	24 (1–100)	20 (1–80)	0.67
Preoperative Chemotherapy regimen				0.94
Anthracycline plus taxane	289 (71.5%)	205 (71.4%)	84 (71.8%)	
Other	115 (28.5%)	82 (28.6%)	33 (28.2%)	
Surgery type				0.36
Breast-conserving	295 (73.2%)	213 (74.5%)	82 (70.1%)	
Mastectomy	108 (26.8%)	73 (25.5%)	35 (29.9%)	
pCR	23 (5.7%)	12 (4.2%)	11 (9.4%)	**0.04**

pCR, Pathological complete response; **IHC**, immunohistochemical staining score.
Values are n (%) unless otherwise specified. IHC 1+/2+ = HER2-low group.
Other histopathological subtypes include lobular and mixed carcinomas.
Boldface values denote statistically significant differences.

Pathologic complete response according to HER2 IHC status

The pCR rate was significantly higher in the HER2-low group (IHC 1+/2+ ISH–) compared with the HER2 IHC 0 group (9.4% [11/117] vs 4.2% [12/287]; χ^2 = 4.22, df=1, p=0.040) (Figure 2), corresponding to an unadjusted odds ratio of 2.38 (95% CI, 1.02–5.55), indicating that tumors with low HER2 expression were more likely to achieve pCR after NACT.

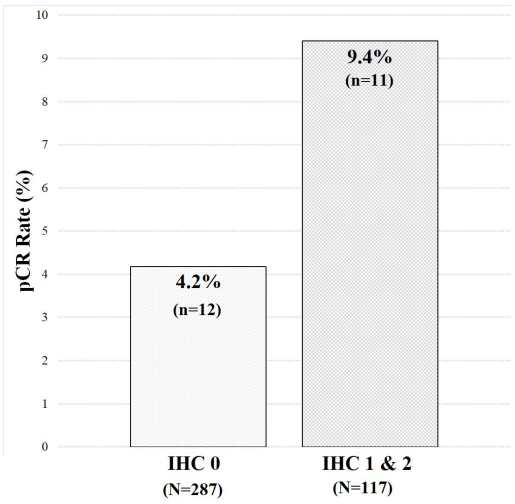


Figure 2:
Pathologic complete response (pCR) rates according to HER2 immunohistochemistry (IHC) status.

In the multivariable logistic regression analysis including age, menopausal status, clinical T and N stage, chemotherapy regimen, and baseline Ki-67 index, HER2-low status (IHC 1+/2+) remained an independent predictor of pCR (OR=2.88, 95% CI=1.17–7.12, p=0.022). A higher Ki-67 index was also significantly associated with an increased likelihood of achieving pCR (OR=1.03 per 1% increase, 95% CI=1.01–1.05, p=0.003). None of the other covariates—including age, menopausal status, clinical T or N stage, and chemotherapy regimen—significantly associated with pCR (all p>0.05) (Table II).

Table II. Multivariable regression analysis for predictors of pathologic complete response (pCR)

Variable	OR	95% CI (Upper - Lower)			p-value
IHC 1+/2+ vs IHC 0 (RC)	2.881	1.165	-	7.122	**0.02**
Ki-67 (per 1% increase)	1.029	1.010	-	1.049	**<0.01**
Age (per year)	0.970	0.905	-	1.039	0.38
Postmenopausal vs Premenopausal (RC)	1.695	0.386	-	7.444	0.48
Clinical N status (positive vs negative [RC])	1.086	0.427	-	2.758	0.86
Clinical T stage (T1–2 vs T3–4 [RC])	2.098	0.582	-	7.563	0.25
Regimen (anthracycline + taxane vs [RC])	0.905	0.329	-	2.490	0.84

OR, odds ratio; **CI**, confidence interval; **RC**, reference category.
Boldface values denote statistically significant differences.

Survival outcomes

The median follow-up duration was 110.2 months (range, 10.5–248.9 months). Median disease-free survival (DFS) and overall survival (OS) were not

reached. At the time of analysis, the 5-year and 10-year DFS rates were 85.1% and 73.7%, respectively, while the corresponding OS rates were 86.4% and 75.3%. Kaplan–Meier survival curves for DFS and OS are presented in Figure 3A and Figure 3B, respectively.

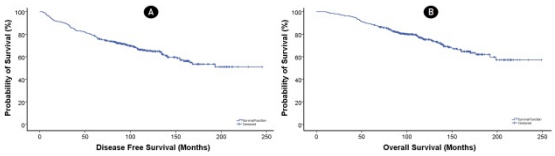


Figure 3:
Kaplan–Meier survival curves for (A) disease-free survival (DFS) and (B) overall survival (OS) in the entire cohort.

In the multivariable Cox proportional hazards model, pathological stage remained the only independent predictor of DFS (HR=2.02, 95% CI=1.55–2.61, p<0.001). Other variables—including HER2 IHC status (1+/2+ vs 0; HR=0.97, 95% CI=0.66–1.43, p=0.861), Ki-67 index (HR=1.01 per 1% increase, 95% CI=1.00–1.02, p=0.050), age at diagnosis (HR=1.01, 95% CI=0.99–1.04, p=0.372), menopausal status (HR=1.06, 95% CI=0.60–1.86, p=0.853), surgery type (HR=1.23, 95% CI=0.83–1.84, p=0.296), and treatment regimen (perioperative anthracycline-taxane vs others; HR=1.05, 95% CI=0.69–1.58, p=0.830)—were not significantly associated with DFS.

Discussion and Conclusion

In this large single-center cohort of hormone receptor (HR)–positive / HER2-negative breast cancer patients treated with neoadjuvant chemotherapy (NACT), we found that tumors with HER2-low expression (IHC 1+/2+ ISH–) achieved a significantly higher rate of pathologic complete response (pCR) compared with HER2-0 tumors. However, this increased chemosensitivity did not translate into a significant improvement in disease-free survival (DFS). Instead, the pathological stage remained the only independent prognostic factor for DFS in multivariate analysis.

These findings refine our understanding of HER2-low biology, suggesting that HER2 expression below the positivity threshold may affect chemosensitivity but not long-term prognosis. This interpretation is consistent with previous reviews and meta-analyses by Schettini et al.[16] and Denkert et al.[17], which emphasized that HER2-low tumors, although biologically distinct, do not consistently demonstrate improved survival outcomes. Furthermore, Tarantino et al.[18] described HER2-low disease as part of a continuous HER2 expression spectrum rather than a discrete subtype, an idea that explains the mixed prognostic signals reported in the literature.

Several retrospective cohorts have suggested modest outcome differences favoring HER2-low disease in HR-positive patients[19-21]. In contrast, other studies—particularly those conducted in the neoadjuvant setting—found no significant difference in pCR or survival between HER2-low (IHC 1+/2+ ISH–) and HER2-IHC 0 groups[13,14,22,23]. Our present analysis aligns with these latter observations, showing that HER2-low tumors, despite slightly higher pCR rates, do not confer a survival advantage in HR-positive disease.

The higher pCR rate we observed in HER2-low tumors (9.4 % vs 4.2 %) mirrors findings from Denkert et al.[24] and Li et al.[25], who demonstrated increased chemosensitivity associated with partial HER2 pathway activation. One plausible explanation involves cross-talk between estrogen receptor (ER) and HER2 signaling pathways, leading to enhanced chemotherapy responsiveness in tumors with intermediate Ki-67 proliferation[26]. Nevertheless, as shown in the CTNeoBC meta-analysis[27], pCR has limited prognostic value in HR-positive disease, unlike in triple-negative or HER2-positive subtypes.

Consequently, the lack of DFS improvement among HER2-low tumors may reflect the dominant prognostic role of endocrine responsiveness and tumor biology, as reported by Prat et al.[28] and Dowsett et al.[29]. In luminal-type tumors, long-term outcome is primarily governed by hormone sensitivity and residual disease rather than chemotherapy response alone.

Our multivariate analysis identified pathological stage as the sole independent predictor of DFS, reaffirming that residual tumor burden after NACT remains the key determinant of recurrence risk. Similar conclusions were drawn by Loibl et al.[30], who emphasized the central prognostic weight of post-treatment stage across early HR-positive breast cancer.

From a clinical perspective, these results highlight that HER2-low status currently carries more therapeutic than prognostic relevance. The recent success of trastuzumab deruxtecan (T-DXd) in the metastatic HER2-low population[5] and its ongoing evaluation in the adjuvant DESTINY-Breast05 trial[31] support HER2-low as a clinically actionable subgroup. Incorporating HER2-low categorization into future adjuvant or neoadjuvant trials with antibody–drug conjugates may help define its role

in the management of early-stage disease. However, the biological continuum hypothesis[15,18,32] suggests that HER2-low tumors may represent the upper spectrum of HER2-negative disease rather than a distinct entity.

Our study's strengths include a homogeneous HR-positive cohort and an extended follow-up exceeding nine years. Nonetheless, certain limitations must be acknowledged. The retrospective design introduces inherent bias; HER2 IHC assessment remains semi-quantitative, and molecular subtyping (e.g., PAM50) was unavailable, which limits deeper biological discrimination between luminal A and luminal B tumors[17,18]. Additionally, potential interobserver variability in HER2-low scoring among pathologists should be acknowledged, as this represents a major challenge for reproducibility and accurate patient classification.

In conclusion, HER2-low tumors exhibited higher chemosensitivity but no independent prognostic advantage in early HR-positive breast cancer. The pathological stage remains the dominant determinant of DFS. These findings support the view that HER2-low represents a biologic continuum rather than a separate prognostic category. Future prospective studies integrating molecular profiling and ADC-based neoadjuvant approaches are warranted to clarify its impact on early-stage treatment and precision oncology.

Researcher Contribution Statement:
Idea and design: A.B.S., T.E., C.K.
Data collection and processing: B.O., M.O. C.K., M.S., B.E.O., E.E.O., Y.K., G.A., H.O.B., A.A.
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Writing of significant parts of the article: A.B.S., C.K., B.O.

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Conflict of Interest Statement:
The authors of the article declare that there is no conflict of interest regarding the content of this study.

Ethics Committee Approval Information:
Approving Committee: Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee
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