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The Role of the NOLUS Score in Predicting pCR and iDFS in HR-positive HER2-negative Early Breast Cancer Patients who Received Neoadjuvant Chemotherapy

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Abstract. *Background/Aim: Breast cancer remains a significant health challenge, with neoadjuvant chemotherapy (NACT) improving clinical outcomes in certain subtypes. However, the role of NACT in hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer is unclear due to various outcomes and generally low rates of pathologic complete response (pCR). This study introduces the Non-Luminal Disease Score (NOLUS) as a potential predictive tool for assessing the response to NACT in these cases. Patients and Methods: We retrospectively assessed patients diagnosed with locally advanced HR+/HER2– breast cancer who received NACT at our institution from 2009 to 2023. The study explored the association between NOLUS and pCR rates. NOLUS was calculated as positive or negative based on the percentage of estrogen receptor, progesterone receptor, and Ki-67 in tumor cells. We also investigated the correlation between pCR and invasive disease-free survival (iDFS), and examined NOLUS positivity across different age groups. Results: A total of 149 patients met the inclusion criteria. NOLUS-positive patients exhibited a significantly higher pCR rate of 33.33% compared to 10.4% in NOLUS-negative patients (p=0.0031). With a median follow-up of 2.47 years, NOLUS-positive patients who achieved pCR had a 100% iDFS rate, mirroring the pCR versus residual disease patterns seen in triple-negative patients. NOLUS positivity was observed in 20.43% of patients aged 22-50, compared to 8.93% in those over 50, though this difference was not statistically significant. Conclusion: NOLUS exhibits potential in predicting pCR in HR+/HER2– breast cancer, serving as a cost-effective substitute for genomic tests.*

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Breast cancer remains a significant health concern for women, with an estimated 300,000 new cases and 43,000 deaths reported in the U.S. for 2023. Of these cases, 63% are diagnosed as localized disease, with an impressive 99% 5-year survival rate (1). However, 25% of these patients will experience a relapse, with distant relapses resulting in incurable disease (2). Extensive efforts have been undertaken in recent decades to enhance survival rates.

The integration of neoadjuvant chemotherapy (NACT) before breast cancer surgery, and the achievement of pathologic complete response (pCR) in the surgical specimen following NACT have significantly influenced clinical outcomes for localized breast cancer (3, 4). Numerous extensive cohort studies and meta-analyses have consistently validated improved long-term results in patients undergoing NACT, particularly those achieving pCR, and especially within triple-negative, human epidermal growth factor 2 (HER2)-positive, or luminal B subtypes (4, 5). However, two meta-analyses did not consistently establish a correlation between pCR and enhanced overall survival (OS) or disease-free survival (DFS) (6, 7). These analyses encountered limitations, including the failure to assess the heterogeneity

of the biological features of the disease and the use of regimens not reflective of current practices. As a result, it is crucial to distinguish how pCR is used as a metric at both the patient-level and trial-level endpoints. The United States Food and Drug Administration (FDA) has proposed incorporating pCR rates as a surrogate marker to assess the efficacy of neoadjuvant treatments, arguing that it reasonably predicts clinical benefits (8). Nevertheless, in the context of hormone receptor (HR)-positive HER2-negative disease, which exhibits lower pCR rates, there is no definitive consensus on the use of neoadjuvant therapy due to variable correlations with patient outcomes. Currently, the application of neoadjuvant therapy in these patients is mainly limited to cases involving large tumors, with the primary goal of reducing tumor size (9, 10).

The discrepancy in achieving pCR stems from the inherent heterogeneity of breast cancer cells (11, 12). Notably, four molecular subtypes have been identified using microarrays (luminal A, luminal B, HER2-enriched, and basal-like), each exhibiting distinct chemosensitivity and prognosis (11, 13). Even within the prevalent estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, HER2-negative subtype, which constitutes the majority of breast cancer cases, approximately 2-3% of ER+ tumors exhibit ER+ and/or PR+ cells at levels below 10% (14). A recent update to the ASCO/CAP guideline recommends categorizing these cases as ER-low positive, emphasizing the scarcity of data regarding the benefits of endocrine therapy in these patients (14, 15).

Additionally, ER-low individuals often exhibit a more aggressive biological profile, sometimes expressing basal markers akin to ER-negative patients, and consistently show poorer DFS in comparison to the ER-high subtype across multiple studies (16, 17). The presence of a basal-like phenotype contributes to the observed chemosensitivity and responsiveness in ER-low breast cancer, as evidenced by studies showing higher pCR rates compared to ER-high cases (17, 18).

In a recent publication, a simplified non-luminal identifier was introduced as the non-luminal disease score (NOLUS). NOLUS was computed based on the expression levels of ER, PR, and Ki-67 through immunohistochemistry, utilizing the formula NOLUS=–0.45×ER%-0.28×PR+0.27×Ki-67%+73.02. Notably, a positive NOLUS value (≥51.38) was deemed significantly associated with non-luminal disease (19). Following these findings, two studies demonstrated that metastatic breast cancer patients with a positive NOLUS show poorer survival than those with a negative NOLUS when undergoing first-line endocrine therapy with or without CDK4/6 inhibitors (20, 21).

This compelling evidence prompted us to investigate the relevance of NOLUS in early breast cancer patients. We aimed to explore its correlation with pCR following neoadjuvant therapy and its impact on invasive disease-free survival (iDFS).

Patients and Methods

This retrospective study was conducted using data from the electronic medical records of the Oncomedicare database, for patients who received neoadjuvant chemotherapy between 2009 and 2023. Patients were included provided they a) had histologically confirmed locally advanced HR-positive HER2-negative breast cancer as defined by immunohistochemistry (IHC) (HER2 0, +1, or +2 with negative in-situ hybridization), b) were aged 18 years or older, and c) underwent NACT followed by surgery. Patients were excluded if any of the following were present: a) lack of sufficient data from the core biopsy regarding estrogen receptor, progesterone receptor, and Ki67 percentage as a continuous value, b) no recorded surgical outcome, and c) diagnosis of HER2-positive disease on the surgical specimen. Histological diagnosis and testing were conducted in laboratories accredited per EN ISO 15189:2021 and actively engaged in External Quality Assurance (EQA) IHC HER2 schemes administered by UKNEQAS and NordiQC. For all histology assessments, ER- and PR- positivity were defined as greater than 1% positive tumor cells following the ASCO/CAP guidelines, HER2 expression was defined according to the 2018 ASCO/CAP guidelines, and quantification of Ki-67 IHC was performed according to the 2011 guidelines established by the International Ki-67 in Breast Cancer working group.

The NOLUS score that was reported by Pascual *et al*. was calculated in all patients on the pre-NACT core biopsy specimen using the following formula: NOLUS (0-100)=–0.45×ER(%)–0.28×PR(%)+0.27×Ki-67(%)+73 (19). In patients with multiple tumors, NOLUS was calculated for each tumor and the higher score was taken into consideration for further analysis. Two groups were distinguished according to the score, the NOLUS-positive (patients with NOLUS score ≥51.38, defining non luminal disease) and the NOLUS negative (patients with NOLUS score <51.38, defining luminal disease).

The primary objective of the study was to assess the correlation between pCR and NOLUS. A secondary objective was to examine the association between pCR and invasive disease-free survival (iDFS), defined as the time between definitive surgery and emergence of invasive disease or death from any cause, in NOLUS-positive (non-luminal) versus NOLUS-negative (luminal) patients. pCR was defined, as per FDA guidelines, by the absence of evidence of invasive disease in both the breast and the axillary lymph nodes (ypT0/Tis ypN0) on the surgical specimen.

All data were collected from January to February 2024 (database lock). According to the methodological features of an observational non-interventional study, all analyses were descriptive, and the results presented should be interpreted as such. All statistical analyses were performed in Thessaloniki, Greece, using GraphPad Prism 10.2 software by Dotmatics. The collection of data for this retrospective study was registered and approved by the Euromedica General Clinic Ethics Committee, with the registration number 1591/14-03-2024.

The Kaplan–Meier method was employed to estimate the median iDFS in patients with luminal and non-luminal diseases, categorized based on their achievement of pCR. Continuous variables are presented as means and range (minimum, maximum), while categorical variables are presented as frequency tables. A Chi-squared test was applied to evaluate the association between the NOLUS and the probability of achieving pCR. Log-rank tests were performed to assess the between-group differences in iDFS.

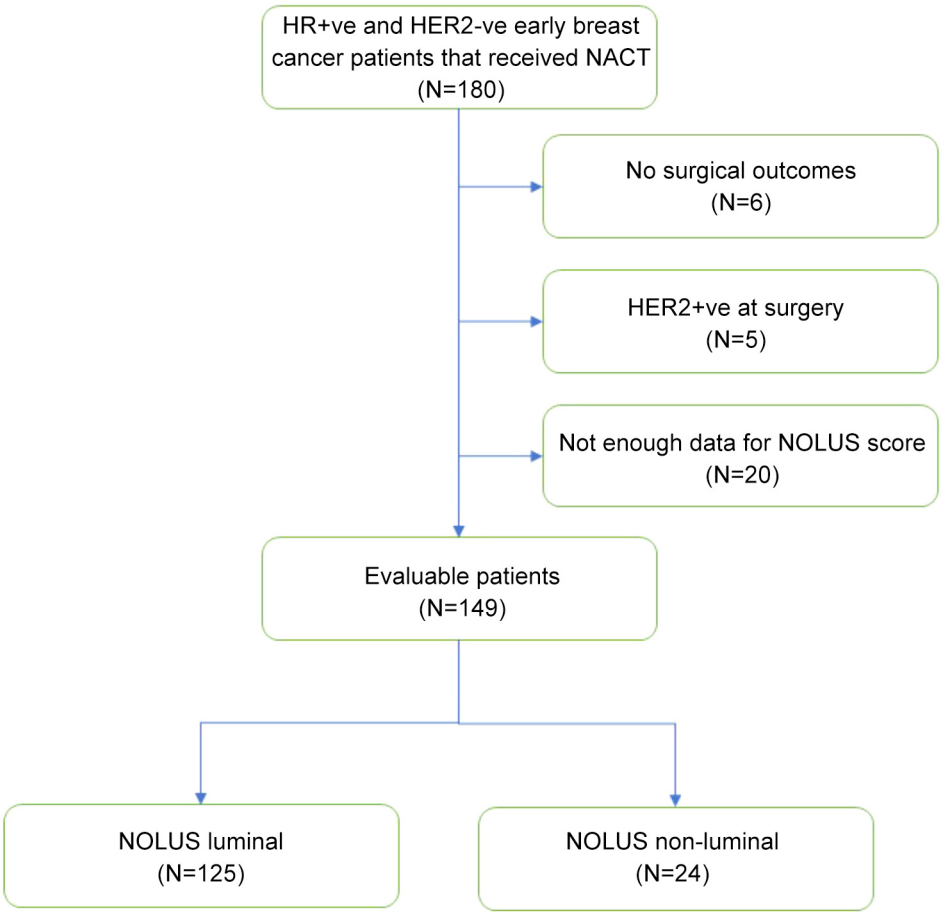

Figure 1. *Study flow chart – CONSORT diagram.*

Results

In this retrospective analysis, data were collected from the medical records of a total of 180 patients diagnosed with HR-positive/HER2 negative breast cancer who underwent NACT at our institution between 2009 and 2023. The median age of the patients was 48 years (range=22-76). The majority of patients presented with invasive ductal carcinoma (IDC) (n=160), while 20 patients had invasive lobular carcinoma (ILC) or mixed histology. The median follow-up period was 2.74 years. Surgical outcomes were available for 174 patients. Of these, twenty patients had insufficient data for NOLUS calculation, and five patients were identified with HER2-positive disease at the time of surgery (Figure 1). Therefore, 149 patients were considered eligible for further analysis. NOLUS was negative in 125 patients, and positive in 24 patients.

NOLUS-positive patients (non-luminal) demonstrated a pCR rate of 33.33%, while NOLUS-negative patients (luminal) demonstrated a pCR rate of 10.4% (p=0.0031) (Figure 2). An analysis of iDFS showed a tendency towards improvement in patients with NOLUS-positive (non-luminal disease) who attained pCR compared to those with residual disease, although statistical significance was not reached. This observed trend was not evident in the NOLUS-negative (luminal) population. Of note, NOLUS-positive patients who obtained pCR achieved a notable 100% incidence of iDFS (Figure 3).

Regarding the type of surgery performed, most patients (55%) underwent lumpectomy, while 40.3% underwent mastectomy. Axillary lymph node dissection was performed in 67.8%, sentinel node biopsy in 16.1%, and targeted axillary dissection in 14.1% of cases (Table I). Regarding treatment regimens for NACT, the majority of patients (147 out of 149) received both anthracycline and taxane-based therapies. Notable combinations included the addition of carboplatin (n=8), immunotherapy (n=4), and bevacizumab (n=3) (Table II).

Subgroup analysis by the precise HER2 status on IHC (HER2-0 and HER2-low) revealed that 19.05% of patients with HER2-0 achieved pCR. In contrast, patients with HER2-low exhibited a lower pCR rate (10.47%). Although the association

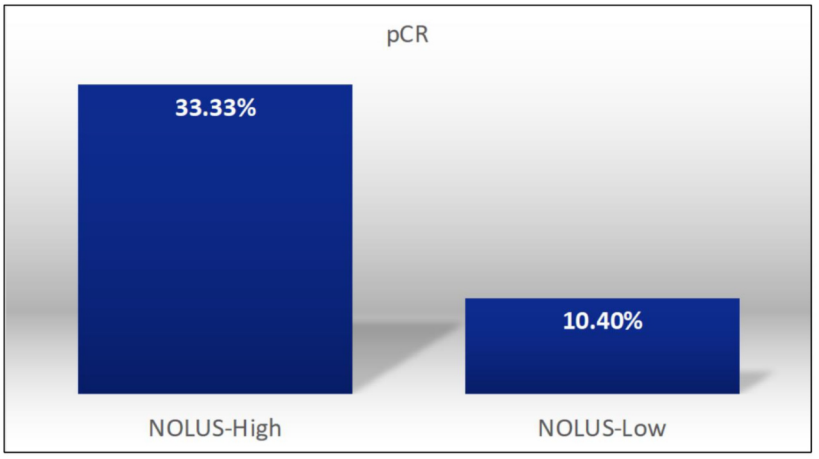

Figure 2. *Complete pathologic response (pCR) rates after neoadjuvant chemotherapy in hormone receptor positive and human epidermal growth factor 2 negative tumors according to Non-Luminal Disease Score (NOLUS) score.*

between HER2 status and pCR outcomes was not statistically significant (p=0.137), when stratifying by luminal status, HER2-low tumors demonstrated a significantly smaller pCR rate, particularly among non-luminal tumors.

In addition, age-related differences in luminal status were observed, with younger patients (22-50 years old) exhibiting a higher likelihood of non-luminal disease (20.43%) compared to older patients (51-76 years old, 8.93%). However, this difference did not reach statistical significance (p=0.0643). There was no observed difference in pCR outcomes according to age.

Discussion

In this retrospective study, we conducted an analysis of 149 patients diagnosed with localized HR+/HER2– breast cancer who underwent neoadjuvant chemotherapy (NACT) using NOLUS. NACT is routinely used in clinical practice in breast cancer subtypes particularly sensitive to chemotherapy, such as HER2-positive or triple negative disease (9). In those cases, the achievement of pCR after NACT is a validated predictor of clinical benefit (4). However, the benefit of NACT in HR+/HER2– disease, which accounts for two-thirds of all breast cancer cases, is not as clear. Numerous studies have consistently shown that the HR+/HER2– subtype is generally less responsive to chemotherapy. Even Luminal B-like patients exhibit a low pCR rate, typically approximately 24.5% with modern regimens including immunotherapy (4, 22-24). This stems from the biological heterogeneity of breast cancer cells among the HR+ subtype, and the lack of a predictive model of NACT benefit in this setting. Therefore, there is no consensus on the use of NACT for HR+/HER2– cancers, and the main indication for its use is the downstaging of large tumors (convert to a breast-conserving surgery or/and avoid axillary lymph node dissection) (9).

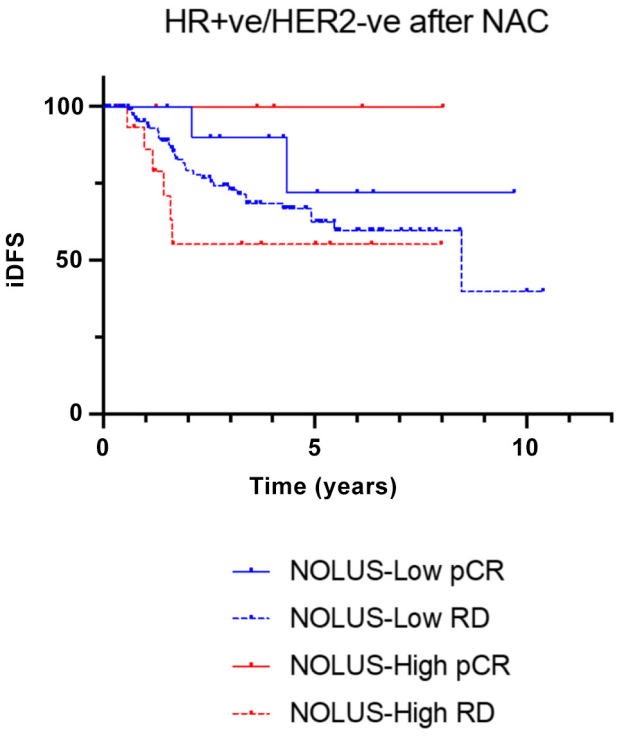

Figure 3. *Invasive disease-free survival (iDFS) in patients that received neo-adjuvant chemotherapy according to Non-Luminal Disease Score (NOLUS) score and pathological response. pCR: Pathological complete response, RD: residual disease.*

For this purpose, we assessed the NOLUS as a predictor of NACT effectiveness. Our findings indicate that NOLUS-positive patients exhibited a higher rate of pCR compared to NOLUS-negative patients. A total of 33.3% of NOLUS-

Table I. *Type of breast surgery in patients who received neoadjuvant chemotherapy.*

Type of breast surgery	n=149 (%)
Lumpectomy	82 (55%)
Mastectomy	60 (40.3%)
Mastectomy and contralateral lumpectomy	1
Bilateral mastectomy	6
Type of axillary surgery	**n=149**
Axillary node clearance (ANC)	101 (67.8%)
Sentinel node biopsy (SNB)	24 (16.1%)
Targeted axillary dissection – no ANC	21 (14.1%)
ANC and contralateral SNB	1 (0.667%)
TAD and contralateral SNB	1 (0.667%)
Not performed	1 (0.667%)

Table II. *Treatment regimens used for neoadjuvant chemotherapy.*

Chemotherapy used	n=149 patients
Anthracycline & Taxane	147
+ Carboplatin	7
+ Bevacizumab	2
+ Bevacizumab + Carboplatin	1
+ Pembrolizumab + Carboplatin	4
Anthracycline only	1
Taxane only	1

positive patients achieved pCR, even without the use of immunotherapy, while only 10.4% of NOLUS-negative patients achieved the same outcome. Furthermore, among the NOLUS-positive patients who attained pCR, prognosis was notably favorable, outperforming not only NOLUS-negative patients (irrespective of their pCR status) but also mirroring the outcomes observed in certain studies involving patients with triple-negative disease (4). The identification of a straightforward and cost-effective predictive tool for evaluating the effectiveness of NACT in this specific subtype of breast cancer remains an unmet medical need, underscoring the significance of our study results.

In recent years, numerous studies have been undertaken to identify a robust predictive tool for assessing response to NACT in ER+/HER2– breast cancer (25-30). Guan *et al*., utilizing real-world evidence, demonstrated that ER, PR, Ki67%, and tumor size independently served as predictive factors for achieving pCR in breast cancer (28). Complementing this finding, a study by Lips and colleagues echoed similar results, emphasizing that PR-negative cancers exhibited a significantly higher likelihood of achieving pCR compared to their PR-positive counterparts (26). Furthermore, a pooled analysis from ten randomized neoadjuvant studies conducted by the German Breast Group revealed an elevated pCR rate (11.2% *vs*. 5.8%, $p<0.001$) in the cohort with tumors that were ER-positive, HER2-negative, and PR-negative. Notably, patients achieving pCR in this cohort also experienced a significant survival benefit ($p<0.001$) (30).

In the last decades, molecular signatures have played a pivotal role in sparing ER+/HER2– patients from unnecessary adjuvant chemotherapy and its associated side effects. These molecular signatures aid in distinguishing patients who benefit from adjuvant chemotherapy from those who do not (10, 31-33). Notably, efforts have been made to extend the application of these signatures to the neoadjuvant phase. Several genomic signatures, such as Oncotype DX, MammaPrint, and EndoPredict, have undergone evaluation to assess their predictive efficacy in predicting pCR following NACT (34-38). In a study conducted by Pease *et al*., it was observed that 9.6% of patients exhibiting a high recurrent score (as per Oncotype DX) attained a pCR. The adjusted odds ratio, accounting for various influencing variables, was found to be 4.8 when compared to the intermediate group, indicating a higher likelihood of achieving pCR (34). Similarly, in a retrospective analysis by Bertucci and colleagues involving 553 patients who underwent NACT and were assessed using the 12-gene signature EndoPredict, a significant difference in pCR rates was noted between the low-risk and high-risk groups (7% *vs*. 17%, $p<0.001$) (38). It is essential to emphasize that all the aforementioned studies reported lower pCR rates compared to our study. Furthermore, the utilization of a genomic test is not universally available and entails a significant cost; in most countries, reimbursement is limited to the adjuvant setting. This observation implies, at the very least, the noninferiority of NOLUS—an approach that is both costless and simpler—in identifying the chemosensitive group within the broader ER+/HER2– breast cancer subtype.

The question of whether patients with HR-positive and HER2-negative disease achieving a pCR after NACT exhibit better survival outcomes than non-pCR patients remains a subject of controversy (4, 6-7, 12, 28, 30, 39). Some studies suggest that within this subtype, individuals with low or absent PR expression and/or high Ki67% levels may face a poorer prognosis. However, when these patients achieve pCR, there is an improvement in survival outcomes (28, 30). Furthermore, a large pooled analysis involving over 9.000 patients with every subtype of breast cancer demonstrated that individuals with ER-positive/HER2-negative/grade 3 disease who achieved pCR exhibited statistically better event-free survival (hazard ratio=0.27). In contrast, patients with ER-positive/HER2-negative/grade 1 or 2 disease did not experience a survival benefit if they achieved pCR (4). Our study confirmed these findings, showing that NOLUS-positive patients with pCR at the time of surgery had a notably favorable prognosis, with 100% iDFS at a median follow-up of 2.74 years, surpassing the outcomes of NOLUS-negative

patients who achieved pCR. The correlation between achieving pCR and iDFS was not statistically significant, although it is important to acknowledge that the sample size for this analysis was small and could have impacted the result. However, certain meta-analyses have not shown a significant survival advantage between patients achieving pCR and those who do not after NACT (6, 7). In a meta-analysis involving over 32,000 patients with breast cancer, Conforti *et al*. did not observe a robust association between pCR and DFS, even when examining various subgroups (6). The controversy observed in different meta-analyses and real-world data on this matter may be influenced by various factors. Specifically, the inherent heterogeneity within the HR+/HER2-negative breast cancer subtype could be a significant contributing factor. Another element to consider is the diversity in neoadjuvant chemotherapy regimens and schedules administered over the years. Furthermore, disparities in the criteria used to classify pCR across various studies may also play a role in intensifying the controversy.

In this study, we also assessed the incidence of NOLUS positivity in distinct age groups. Younger patients (aged 22-50 years) were more prone to non-luminal disease (NOLUS-positive) compared to older individuals (aged 51-76 years), although this difference also did not reach statistical significance. Furthermore, no disparity in pCR rates was discerned between these age groups.

There are some limitations in this study. The predominant one is its retrospective nature, making it susceptible to inherent biases associated with the study design. Additionally, the assessment of ER, PR, and Ki67 was not conducted centrally in a single laboratory; instead, IHC data was extracted from local pathology reports. Moreover, neither NOLUS nor the biomarkers constituting NOLUS (namely ER, PR, and Ki67) are standardized, leading to a lack of standardization in NOLUS calculation.

In conclusion, our assessment of NOLUS as a tool for identifying the subgroup of HR+/HER2-negative patients with locally advanced breast cancer prone to achieving pCR highlights that non-luminal disease exhibits statistically higher pCR rates. The utilization of the NOLUS score proves to be a valuable tool in identifying patients with HR+/HER2-negative breast cancer who may derive significant benefits from neoadjuvant chemotherapy, potentially surpassing the performance of molecular assays. However, it is imperative to note that large prospective studies are warranted to delve deeper into the clinical utility and validity of NOLUS. These investigations will pave the way for integrating NOLUS into everyday clinical practice.

Conflicts of Interest

A-LA and GD declare no relevant conflict of interest. LK has received honoraria and consultancy fees from Ipsen, BMS, Janssen, MSD and Amgen. IN has received honoraria from Roche. KP has received honoraria and consultancy fees from MSD, Gilead, AstraZeneca, Novartis, Eli Lilly, Roche and GSK and Research Funding from Roche, Novartis, Daiichi Sankyo, Eli Lilly, AstraZeneca, BMS, Boehringer and EISAI.

Authors' Contributions

Manuscript preparation: A-LA, GD, KP; Concept and design: A-LA, KP; Collection of data: A-LA, LK, IN, KP; Statistical analysis: A-LA, KP; Manuscript reviewing and corrections: All Authors.

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