Histopathological Grade as a Prognostic Marker in de novo Metastatic HER2-Positive Breast Cancer Treated with First-Line Docetaxel, Trastuzumab, and Pertuzumab

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BACKGROUND

The TPH regimen (docetaxel, trastuzumab, pertuzumab) has long been the standard first-line treatment for HER2-positive metastatic breast cancer (MBC). However, recent findings from the DESTINY-Breast09 trial have challenged this paradigm, underscoring the need for predictive biomarkers to personalize treatment selection. Estrogen receptor positivity (ER+) may inform the use of CDK4/6 inhibitors, such as palbociclib, during the maintenance phase. While molecular classifiers—such as ERBB2 expression within the HER2Dx signature—have shown promise in identifying patients likely to benefit from prolonged TPH treatment, the prognostic potential of routinely available histopathological parameters remains insufficiently explored. This study aimed to evaluate whether histological grade, Ki67 proliferation index, and ER status predict progression-free survival (PFS) in patients receiving first-line TPH.

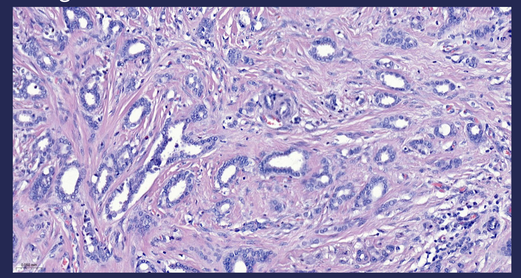


***Figure 1**. Tumor grading assessment (grade 1); nuclear features 2, mitotic activity 1, and tubular formation 2 (20× magnification).*

MATERIALS/METHODS

We conducted a retrospective analysis of 134 female patients with de novo HER2-positive MBC, treated with first-line TPH between 2017-2024, all of whom had available breast tumor biopsy samples for histopathological evaluation. The median age was 60.2 years (range, 27.1-84.3 years). ECOG performance status was 0 in half of the patients, while the other half had a status of 1 or 2. Oligometastatic disease (OMD, ≤5 metastatic lesions) was present in 46.3%, liver metastases in 32.8%, and lung metastases in 24.6%. Histological grade was G1 in 2.2%, G2 in 44.8%, and G3 in 53.0%; G1 and G2 were grouped as G1-2. ER positivity was observed in 55.2% of cases, and the median Ki67 was 32% (IQR: 20-60%). Prognostic factors were assessed using Cox proportional hazards models; variables with p<0.2 in univariate analysis were included in the multivariate model.

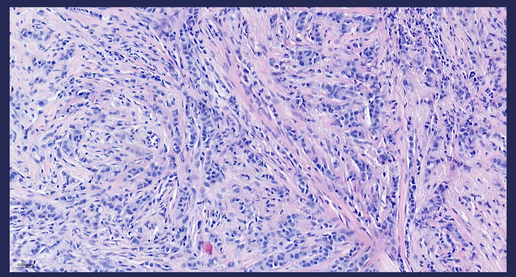


***Figure 2**. Tumor grading assessment (grade 2): nuclear features 2, mitotic activity 1, and tubular formation 3 (20× magnification).*

RESULTS

The median PFS in the entire cohort was 38.3 months. Histological grade correlated strongly with outcome: patients with G1-2 tumors had a median PFS of 79.1 months versus 25.2 months for those with G3 tumors. The 2-year PFS rate was 71.2% (95% CI: 57.7-81.1%) for G1-2 and 52.1% (95% CI: 39.7-63.2%) for G3. In univariate analysis, G3 grade (HR 1.93; 95%CI: 1.05-3.53; p = 0.034) and OMD (HR 0.49; 95% CI: 0.29-0.81; p = 0.006) were significantly associated with PFS. ER-positive status (HR 0.65; 95% CI: 0.38-1.11; p = 0.115) and Ki-67 index (HR 1.01; 95% CI: 0.996-1.021; p = 0.178) met the threshold for inclusion in multivariate analysis. In the multivariate model, both OMD and G3 grade remained independently associated with PFS. High histological grade was confirmed as a significant negative prognostic factor (HR 2.40; 95% CI: 1.08-5.28;p = 0.030).

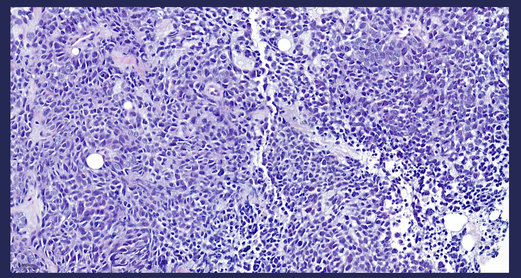
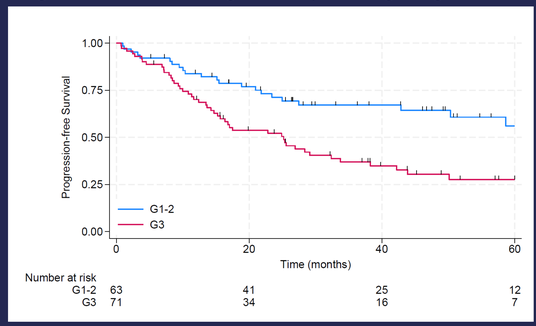


***Figure 3**. Tumor grading assessment (grade 3): nuclear features 3, mitotic activity 3, and tubular formation 3 (20× magnification).*

***Figure 4.** PFS according to histopathological grade.*



CONCLUSIONS

Histological grade emerged as an independent prognostic factor, whereas ER status and Ki67 did not reach statistical significance. This finding highlights the prognostic relevance of traditional histopathological features in de novo HER2-positive MBC treated with TPH. High-grade tumors were associated with significantly shorter PFS, suggesting the need for intensified or alternative therapeutic strategies in this subgroup. While histopathology offers valuable prognostic insights, molecular profiling holds the potential to deliver a deeper biological understanding and enables more precise treatment stratification in this heterogeneous disease.

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MK COI: Clinical Trials: Roche, MSD, Novartis, Seagen, Gilead; Travel grants: Roche, Novartis, Pfizer, Swixx Biopharma Teva, Amgen, MSD, Gilead, ASTRAZENECA; Speakers Bureau: Novartis, Roche, Pfizer, Lilly, Teva, Amgen, Swixx Biopharma, Gilead, MSD, astrazeneca; Advisory board: Novartis, Gilead