Association Between Human Epidermal Growth Factor Receptor 2-Low Status and Time to Development of Brain Metastases Among Patients With Breast Cancer: A Retrospective Cohort Study

Kevin Yijun Fan, MD[1,2]; Rania Chehade, MD, MSc[1,2]; Italo Fernandes, MD[1,2]; Veronika Moravan, MSc[3]; Arjun Sahgal, MD, FRCPC[1,2]; Ellen Warner, MD, MSc, FACP, FRCPC[1,2]; and Katarzyna Joanna Jerzak, MD, MSc, FRCPC[1,2]

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ABSTRACT

PURPOSE Human epidermal growth factor receptor 2 (HER2)-low is a newly defined subgroup of HER2-negative breast cancer. It is unknown whether HER2-low status is associated with brain metastases (BrM) development. We aimed to determine the association between HER2-low status and the time to developing BrM.

METHODS HER2 status was determined in a cohort of 689 women with metastatic breast cancer (MBC) who underwent treatment for BrM at Sunnybrook Odette Cancer Centre from 2008 to 2018. In patients with primary breast cancer (PBC) HER2 subclassification available (subgroup 1), we investigated time from PBC diagnosis to BrM diagnosis (PBC-time to brain metastases [TTBM]). In patients with HER2 subclassification available in any tissue (subgroup 2), we investigated time from MBC diagnosis to BrM diagnosis (MBC-TTBM).

RESULTS In subgroup 1 (n = 175), patients with HER2-low disease (n = 42) had a shorter PBC-TTBM compared with those with HER2-zero disease (n = 77; hazard ratio, 2.4; P = .0003). When stratified by hormone receptor (HR) status, this observation held true in the HR+/HER2− population, but not in the triple-negative breast cancer (TNBC) population. In subgroup 2 (n = 279), patients with HER2-low disease (n = 53) had a shorter MBC-TTBM compared to those with HER2-zero disease (n = 44) in the HR+/HER2− population (hazard ratio, 1.55; P = .036); however, this did not hold true in the TNBC population. Likelihood ratio test revealed significant interaction between HER2 and HR status in subgroup 2 (P = .016), but not subgroup 1 (P = .21).

CONCLUSION Our findings suggest that among patients with HR+ breast cancer, HER2-low status was associated with shorter TTBM compared with HER2-zero status. In a subset of patients for whom HER2 status of the PBC was available, HER2-low status was associated with shorter PBC-TTBM, irrespective of HR status. This study suggests a previously unrecognized association between HER2-low status and timing of BrM development.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Breast cancer is the second most common cause of brain metastases (BrM),[1] which are associated with significant morbidity and mortality. The lifetime risk of developing BrM is associated with breast cancer subtype, previously reported to be 15% among patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) metastatic breast cancer (MBC); the risk of developing BrM was approximately double among those with triple-negative breast cancer (TNBC) or HER2-positive (HER2+) disease.[2,3]

HER2 is a transmembrane receptor tyrosine kinase that is overexpressed in 15%-20% of breast cancers.[4] Through homo- and heterodimerization, it activates downstream signaling pathways associated with proliferation, invasion, and cancer cell survival, and its expression is associated with poor clinical outcomes.[4,5] HER2+ is defined as immunohistochemistry (IHC) 3+ or 2+ with positive in situ

CONTEXT

Key Objective

To determine if human epidermal growth factor receptor 2 (HER2)-low status is associated with timing of brain metastases (BrM) development among patients with metastatic breast cancer (MBC).

Knowledge Generated

In a retrospective Canadian cohort of patients with MBC treated for BrM, among patients with hormone receptor (HR)–positive breast cancer, HER2-low status is associated with shorter time to BrM compared with HER2-zero status. In a subset of patients for whom HER2 status of the primary breast cancer (PBC) was available, HER2-low status was associated with shorter time from PBC to BrM, irrespective of HR status.

Relevance

This study suggests a previously unrecognized association between HER2-low status and timing of BrM development. Once validated, this may help identify patients with MBC who may benefit from surveillance and/or therapeutic intervention to prevent or delay BrM.

hybridization (ISH), whereas, until recently, all other breast cancers were classified as HER2–. This latter group is now further subclassified as HER2-low (either IHC 1+ or IHC 2+ and ISH-negative) or HER2-zero (IHC 0). Although only patients with HER2+ breast cancer benefit from trastuzumab, the recent advent of antibody-drug conjugates (ADCs) targeting HER2 such as trastuzumab deruxtecan (T-DXd) have demonstrated an opportunity to improve overall survival in patients with HER2-low MBC, as demonstrated by the phase III DESTINY-Breast04 trial.[6] Furthermore, 29% of breast cancer BrM are HER2-low,[7] and T-DXd has been shown to have robust intracranial efficacy.[8]

Although there has been a recent shift toward routinely identifying HER2-low MBC cases to predict benefit from T-DXd, it is not yet known whether HER2-low status is associated with the development of BrM. The purpose of this study was to investigate the association between the extent of HER2 expression (HER2+, HER2-low, or HER2-zero) and time to development of BrM in a retrospective cohort of patients with breast cancer.

METHODS

We investigated a retrospective cohort of 689 women with MBC treated at Sunnybrook Odette Cancer Centre (Toronto, Canada) with surgery or radiotherapy for BrM between 2008 and 2018.

We defined subgroup 1 as all patients for whom a pathological report of HER2 subclassification was available for the primary breast cancer (PBC; Appendix Fig A1). HER2 status in this study was defined on the basis of IHC and ISH reported at the time of initial pathology review. In subgroup 1, we investigated time from PBC diagnosis to time to developing BrM (PBC-time to brain metastases [TTBM]), measured as a continuous variable, in relation to HER2 status of the PBC using Kaplan-Meier analysis.

We defined subgroup 2 as all patients for whom a pathological report of HER2 subclassification was available for any tissue (PBC, MBC, and/or BrM; Appendix Fig A1). In patients with more than one biopsy with HER2 testing available, HER2 status was assigned on the basis of the biopsy with the higher HER2 status. In subgroup 2, we investigated time from MBC to time to developing BrM (MBC-TTBM), measured as a continuous variable, in relation to HER2 status using Kaplan-Meier analysis.

Of note, a number of patients in the overall cohort were reported to have HER2+ or HER2– breast cancer on the basis of clinical reports without details regarding HER2 IHC or ISH status (as pathological reports were not accessible for some patients who were referred from other centers). Such patients were excluded from subgroups 1 and 2, as it was not possible to determine whether the patients with HER2– breast cancer had HER2-low or HER2-zero disease.

Paired sample analysis of HER2 status across metastatic sites was performed using Cohen's kappa to evaluate correlation and McNemar-Bowker's test and binomial test to evaluate for directional change. Kaplan-Meier curves were generated for PBC-TTBM and MBC-TTBM, with log-rank test used to ascertain differences between curves. Cox proportional hazards multivariable analysis (MVA) was performed to evaluate two covariates (HER2 status and HR status) associated with PBC-TTBM and MBC-TTBM. A likelihood ratio test (LRT) was performed to assess the interaction between the two covariates. All testing used the traditional significance level of $\alpha = .05$. Analyses were performed using R software package, version 4.3.1 (R Core Team 2023, R Foundation for Statistical Computing, Vienna, Austria).

This project was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, which determined that an Informed Consent Form is not required for participants of this study; consent requirements, if applicable, have been otherwise dealt with in accordance with Article 3.7 and/or 3.12 and/or 5.5 of the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Tri-Council Policy Statement 2).

RESULTS

Patient characteristics in the overall cohort, subgroup 1, and subgroup 2 are summarized in Table 1. Among the full cohort of 689 patients, the median age at BC diagnosis was 51 years (range, 23-87 years) and 489 (71%) had metachronous metastatic disease (ie, MBC diagnosed >6 months from PBC diagnosis). In subgroup 1 (n = 175), 56 patients (32%) had HER2+ disease, 42 (24%) HER2-low disease, and 77 (44%) HER2-zero disease. In subgroup 2 (n = 279), 119 patients (43%) had HER2+ disease, 78 (28%) HER2-low disease, and 82 (29%) HER2-zero disease.

When comparing paired samples from patients in whom HER2 status was available in both the PBC and a metastatic site, HER2 status was generally higher in the extracranial metastatic site (n = 61, McNemar-Bowker $P = .023$, Cohen's $\kappa = 0.60$; Appendix Fig A2A) and BrM (n = 14, binary test $P = .004$, Cohen's $\kappa = 0.21$) compared with the matched PBC (Appendix Fig A2B). Among patients with distant extracranial metastatic disease (n = 592 of 689 patients), those with bone-only metastases (n = 80) and those with visceral (ie, lung or liver) metastases (n = 512) had a similar MBC-TTBM (Appendix Fig A3).

In subgroup 1 (n = 175), the median PBC-TTBM was 31 (IQR, 17-77) months. The median PBC-TTBM was 26 (IQR, 23-29) months in those with TNBC (n = 49), 35 (IQR, 24-56) months in those with HER2+ disease (n = 56), and 46 (IQR, 33-69) months in those with HR+/HER2− disease (n = 70; $P = .14$; Fig 1A). Among those originally classified as having HER2− disease, the median PBC-TTBM was 23 (IQR, 18-35) months in those with HER2-low disease (n = 42) and 37 (IQR, 27-67) months in those with HER2-zero disease (n = 77; $P = .01$; Fig 1B). Among the smaller HR+/HER2− (n = 70) subgroup, those with HER2-low disease (n = 30) had a significantly shorter PBC-TTBM compared with those with HER2-zero disease (n = 40; 23 [IQR, 17-42] *v* 87 [IQR, 52-116] months; $P < .0001$; Fig 1C). In the subgroup with TNBC (n = 49), those with HER2-low disease (n = 12) did not have a significantly different PBC-TTBM compared to those with HER2-zero disease (n = 37; 24 [IQR, 15-not releasable [NR]] *v* 27 [IQR 23-31] months; $P = .69$; Fig 1D). An LRT for the interaction term between the HER2 status and the HR status was not significant ($P = .21$), and on MVA, HER2-low status was independently associated with shorter PBC-TTBM compared with HER2-zero status (hazard ratio, 2.4 [95% CI, 1.5 to 4.0]; $P = .0003$; Appendix Table A1). Furthermore, PBC-TTBM was similar among patients with HER2 1+ (n = 30) and HER2 2+ (n = 12) disease with a median PBC-TTBC of 26 months (95% CI, 18 to 47 months) and 20 months (95% CI, 9.0 months to NR), respectively ($P = .63$).

In subgroup 2 (n = 279), the median MBC-TTBM was 9.0 (IQR, 0-30) months. The median MBC-TTBM was 5.0 (IQR, 1.0-9.0) months in those with TNBC (n = 65), 10 (IQR, 5.4-18) months in those with HER2+ disease (n = 119), and 15 (IQR, 8.0-24) months in those with HR+/HER2− disease (n = 95; $P = .015$; Fig 2A). Among those originally classified as having HER2− disease, the median MBC-TTBM was 8.0 (IQR, 5.0-13) months in those with HER2-low disease (n = 78) and 8.5 (IQR, 6.0-17) months in those with HER2-zero disease (n = 82; $P = .87$; Fig 2B). In the HR+/HER2- subgroup (n = 97), those with HER2-low disease (n = 53) had a shorter MBC-TTBM compared to those with HER2-zero disease (n = 44; 8.0 [IQR, 4.0-21] *v* 21 [IQR, 9.0-40] months; $P = .037$; Fig 2C). Among patients originally classified as having TNBC (n = 63), patients with HER2-low disease (n = 25) did not have significantly different MBC-TTBM compared to those with HER2-zero disease (n = 38; 6.1 [IQR, 0.0-15] *v* 3.0 [IQR, 0.59-9.0] months; $P = .18$; Fig 2D). An LRT for the interaction term between HER2 status and HR status was statistically significant ($P = .016$). MBC-TTBM was similar among patients with HER2 1+ (n = 35) and HER2 2+ (n = 43) disease, with a median MBC-TTBC of 9.0 months (95% CI, 0.0 to 21 months) and 8.0 months (95% CI, 4.0 to 29 months), respectively ($P = .16$).

In total, 162 of 689 patients had LMD, 46 of 175 patients in subgroup 1, and 70 of 279 patients in subgroup 2. HER2 status (HER2-zero, HER2-low, and HER2+) was not associated with the presence or absence of LMD as evaluated by the chi-square test (subgroup 1 $\chi^2 = 0.42$; $P = .81$; subgroup 2 $\chi^2 = 2.9$; $P = .23$).

DISCUSSION

In this single-institution retrospective study, we observed that among patients with HR+ breast cancer, HER2-low status was associated with early development of BrM compared with HER2-zero status. In a subset of patients for whom HER2 status of the PBC was available, HER2-low status was associated with shorter time PBC-TTBM, irrespective of HR status. This study raises the question of whether HER2-low status plays a biological role in driving earlier intracranial metastogenesis. However, given that all patients in our cohort had BrM, further studies are needed to investigate whether HER2-low status is indeed associated with an increased likelihood of BrM development.

In addition to predicting clinical benefit from HER2-directed ADCs, the prognostic significance of HER2-low status has also been investigated. In previous retrospective studies, the survival among patients with HER2-low disease was similar to those with HER2-zero disease, after adjusting for HR expression.[9-11] However, there is conflicting evidence as to whether HER2-low breast cancer has unique biological and

TABLE 1. Baseline Characteristics

Characteristic	Entire Cohort (N = 689)	Subgroup 1 (n = 175)	Subgroup 2 (n = 279)
Age at EBC diagnosis, median (range)	51 (23-87)	49 (26-82)	48 (23-82)
Metastatic disease presentation, No. (%)			
Metachronous	489 (71)	129 (74)	213 (76)
Synchronous	200 (29)	46 (26)	66 (24)
Breast cancer subtype, No. (%)			
HER2+[a]	182 (26)	56 (32)	119 (43)
HR+/HER2−	240 (35)	70 (40)	95 (34)
HR+/HER2 zero	Unknown	40 (23)	43 (15)
HR+/HER2 low	Unknown	30 (17)	52 (19)
TNBC	156 (23)	49 (28)	65 (23)
HR−/HER2 zero	Unknown	37 (21)	39 (14)
HR−/HER2 low	Unknown	12 (7)	26 (9)
Unknown	111 (16)	0	0
Location of extracranial metastases, No. (%)			
Bone	470 (68)	126 (72)	189 (68)
Liver	373 (54)	86 (49)	144 (52)
Lung	386 (56)	108 (62)	167 (60)
Lymph nodes	424 (62)	116 (66)	179 (64)
Number of BrM, No. (%)			
1	86 (12)	21 (12)	43 (15)
>1	387 (56)	107 (61)	150 (54)
Unknown	216 (31)	47 (27)	86 (31)
Leptomeningeal disease, No. (%)			
Yes	162 (24)	46 (26)	70 (18)
No	527 (76)	129 (74)	229 (82)
Symptoms at BrM presentation, No. (%)			
Yes	531 (77)	141 (81)	225 (81)
No	117 (17)	28 (16)	46 (16)
Unknown	41 (6)	6 (3)	8 (4)
Systemic therapy, No. (%)			
HER2-directed	102 (15)	36 (21)	52 (19)
Chemotherapy	246 (36)	90 (51)	125 (45)
Endocrine therapy	100 (15)	21 (12)	46 (16)
Other	10 (1)	2 (1)	3 (1)
No treatment	5 (1)	3 (1)	3 (1)
Unknown	311 (40)	42 (24)	74 (27)

NOTE. Other systemic therapy (n = 10): targeted therapy excluding HER2-directed agents and CDK4/6 inhibitors (n = 5), blinded clinical trial with additional systemic therapy agent (n = 4), and immunotherapy (n = 1).

Abbreviations: BrM, brain metastasis; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HER2−, HER2-negative; HER2+, HER2-positive; HR, hormone receptor; HR−, HR-negative; HR+, HR-positive; TNBC, triple-negative breast cancer.

[a]HER2 status of the overall cohort was defined based on a combination of clinical reports and pathological reports; HER2 status of subgroup 1 was defined based on pathological reports of the primary breast cancer; HER2 status of subgroup 2 was defined based on pathological reports of any biopsy site.

phenotypic features,[12] and very limited evidence has been reported specifically to its metastatic potential to the brain. In a study by Tarantino et al,[13] no significant differences in genomic alterations or tumor mutational burden were observed when comparing next-generation sequencing results between HER2-low and HER2-zero breast cancer. Schettini et al[9] observed that ERBB2 and luminal-related genes were more highly expressed in HER2-low versus HER2-zero HR+ breast cancers; however, they did not observe such differences in TNBC. Preclinical studies have shown that HER2 signaling induces epithelial-mesenchymal transition[14] and promotes matrix metalloprotease–dependent migration through the blood-brain-barrier[15] to increase metastatic potential and brain trophism.[16,17] Since various breast cancer

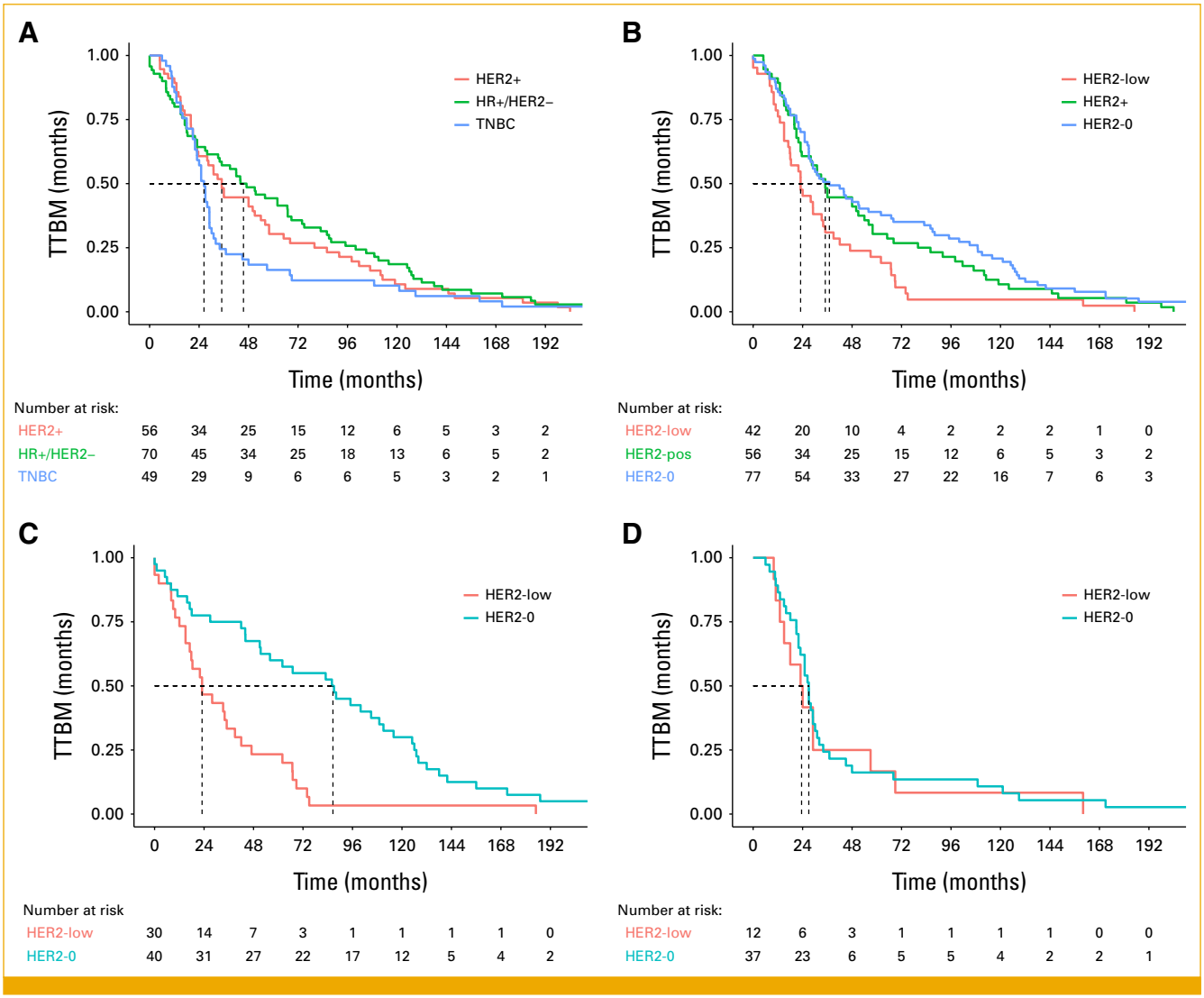

FIG 1. Time from primary breast cancer diagnosis to brain metastasis diagnosis in subgroup 1 stratified by (A) breast cancer subtype, (B) HER2 status, (C) HER2 status among patients with HR+/HER2− disease, and (D) HER2 status among patients with TNBC. HER2, human epidermal growth factor receptor 2; HER2−, HER2-negative; HER2+, HER2-positive; HR+, hormone receptor-positive; TNBC, triple-negative breast cancer; TTBM, time to brain metastases.

subtypes with different levels of HER2 expression are encompassed under the heterogeneous HER2-low category, it remains an open question as to whether a subset of these patients may exhibit HER2-driven brain trophism in a mechanism comparable with that exhibited by HER2+ breast cancer. Our observation that patients with HER2-low breast cancer had a shorter TTBM compared with HER2+ breast cancer does not initially appear consistent with the above hypothesis. However, this may be explained by the fact that most patients with HER2+ disease received HER2-directed therapy, whereas no patients with HER2-low disease received HER2-directed therapy in our study.

BrM as a first site of metastatic recurrence occurs in approximately 5%-10% of patients who receive neoadjuvant chemotherapy for TNBC or HER2+ breast cancer, irrespective of treatment response.[18,19] However, biomarkers associated with the development of BrM among patients with early-stage breast cancer are lacking. A biomarker signature that predicts development of BrM among patients with early-stage breast cancer would be highly desirable in developing clinical trials related to treatment escalation/BrM prevention and surveillance neuroimaging.

Our observation that HER2-low status is associated with a shorter TTBM among patients with HR+ disease is intriguing. In HR+ breast cancer, there is significant crosstalk between HER2 and estrogen receptor (ER) signaling, whereby HER2 overactivation induces downregulation of ER-regulated transcription and resistance to hormone therapy, and conversely, HER2 blockade leads to activation of ER-regulated transcription.[20] Future studies are needed to

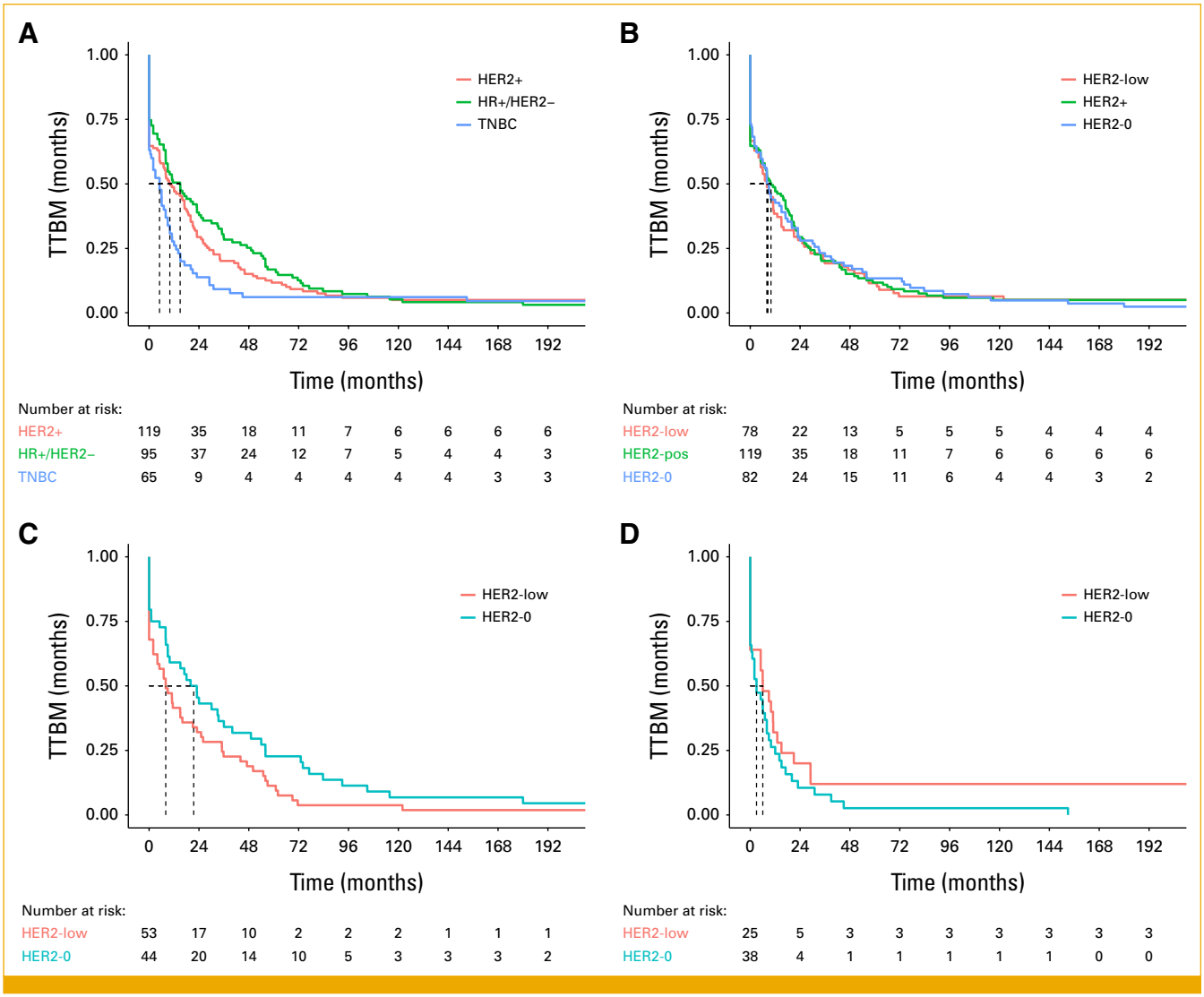

FIG 2. Time from metastatic breast cancer diagnosis to brain metastasis diagnosis in subgroup 2, stratified by (A) breast cancer subtype, (B) HER2 status, (C) HER2 status among the patients with HR+/HER2− disease, and (D) HER2 status among patients with TNBC. HER2, human epidermal growth factor receptor 2; HER2−, HER2-negative; HER2+, HER2-positive; HR+, hormone receptor-positive; TNBC, triple-negative breast cancer; TTBM, time to brain metastases.

investigate whether HER2-driven brain trophism is affected by ER signaling. On the other hand, in TNBC there are additional pathways, independent of HER2 signaling, through which cancer cells invade the stromal and basement membrane and form a more permeable blood-brain-barrier[17,21]; this could potentially explain why patients in our study with TNBC had early development of BrM regardless of HER2 status.

This study has a number of limitations. All patients in this cohort developed BrM, leading to an over-representation of TNBC and HER2+ breast cancer. Given that patients with TNBC are less likely to have HER2-low disease than those historically classified as having HR+/HER2− disease,[22] this may explain the relatively low proportion of patients with HER2-low tumors in our cohort. In addition, a pathological report of HER2 status was not available for many patients, particularly those who were referred from external centers. Furthermore, HER2 status was derived based on original pathological reports that used different versions of ASCO/College of American Pathologists guidelines according to the time of HER2 testing, and it was not possible to repeat the HER2 testing due to limited access to archival tissue. Finally, this study was conducted during a time when T-DXd was not approved for use in HER2-low MBC.

In conclusion, in this single-institution retrospective study, we observe that patients with HER2-low breast cancer developed BrM earlier than those with HER2-zero disease, particularly in the subgroup of patients with HR+ disease. These data are hypothesis-generating and, if validated, may reveal a window of opportunity for therapeutic intervention to prevent and/or delay BrM in patients with HER2-low breast cancer.[23]

AFFILIATIONS

[1]University of Toronto, Toronto, ON, Canada
[2]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada
[3]VM Stats, Toronto, ON, Canada

CORRESPONDING AUTHOR

Katarzyna Joanna Jerzak, MD, MSc, FRCPC; e-mail: katarzyna.jerzak@sunnybrook.ca.

EQUAL CONTRIBUTION

R.C. and I.F. contributed equally.

PRIOR PRESENTATION

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/PO-24-00641. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conception and design: Kevin Yijun Fan, Rania Chehade, Italo Fernandes, Arjun Sahgal, Ellen Warner, Katarzyna Joanna Jerzak
Administrative support: Katarzyna Joanna Jerzak
Provision of study materials or patients: Arjun Sahgal, Katarzyna Joanna Jerzak
Collection and assembly of data: Kevin Yijun Fan, Rania Chehade, Italo Fernandes, Veronika Moravan, Katarzyna Joanna Jerzak
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

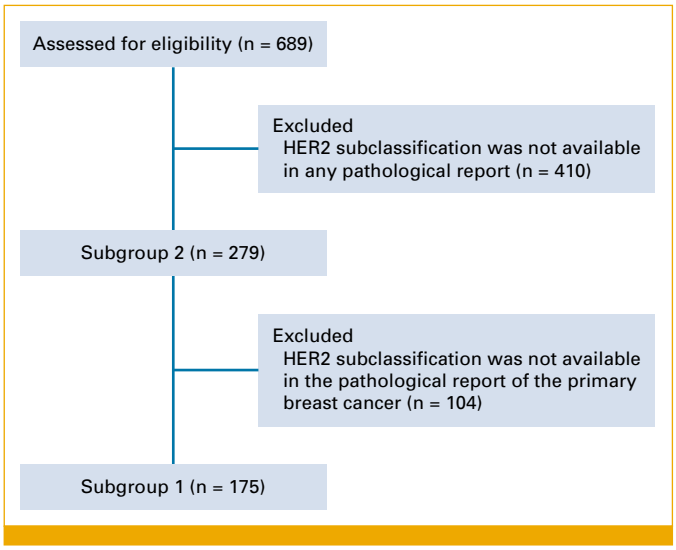

FIG A1. Patient selection. HER2, human epidermal growth factor receptor 2.

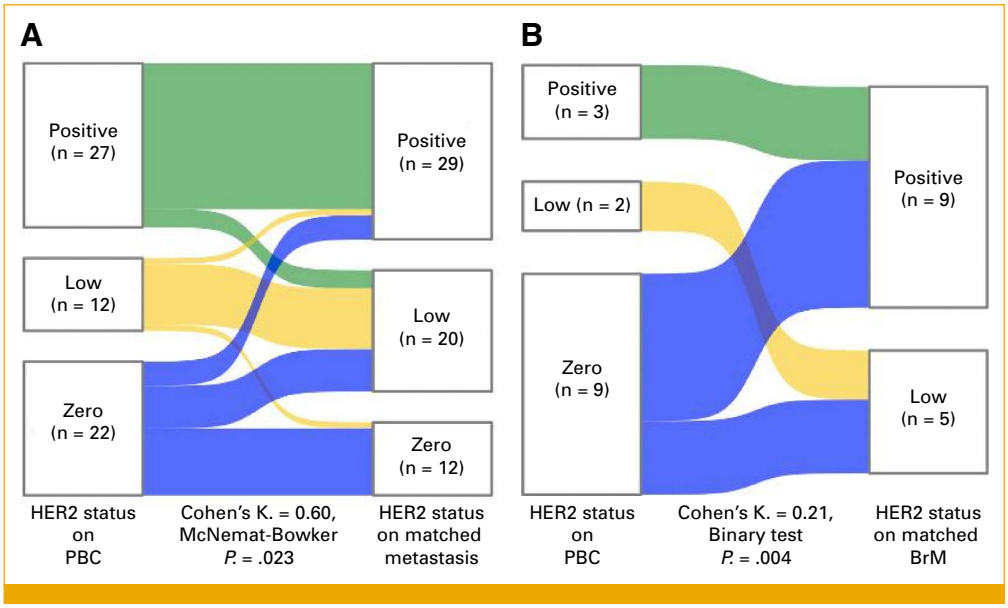

FIG A2. Dynamics of HER2 status across biopsies of PBC and matched extracranial metastases (A), PBC and BrM (B). BrM, brain metastases; HER2, human epidermal growth factor receptor 2; PBC, primary breast cancer.

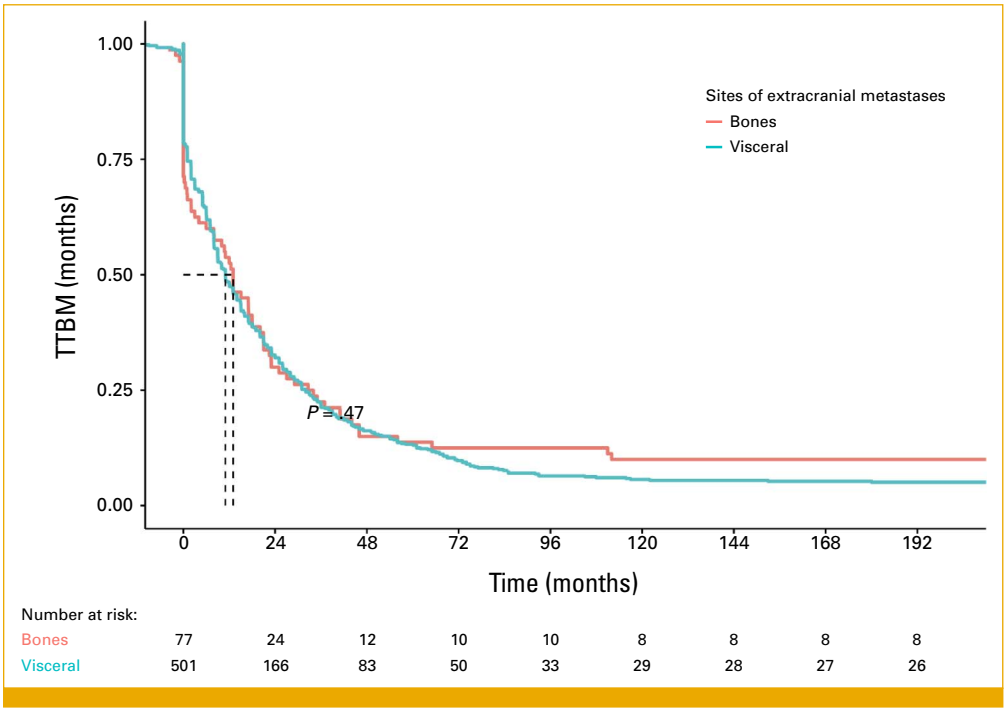

FIG A3. Time from metastatic breast cancer diagnosis to BrM diagnosis by location of extracranial metastases. BrM, brain metastases.

TABLE A1. Cox Proportional Hazards Analysis

Subgroup 1 (n = 175)	Hazard Ratio (95% CI)	*P*
HER2-zero (ref)	1	
HER2-low	2.4 (1.5 to 4.0)	.0003
HER2+	1.3 (0.84 to 2.1)	.21
HR+ (ref)	1	
HR−	1.9 (1.2 to 3.0)	.0058

Subgroup 2 (n = 279)	Hazard Ratio (95% CI)	*P*
HR+/HER2-zero (ref)	1	
HR+/HER2-low	1.6 (1.0 to 2.3)	.036
HR+/HER2+	1.2 (0.9 to 1.8)	.27
HR−/HER2-zero	2.4 (1.5 to 3.8)	.0001
HR−/HER2-low	1.5 (0.9 to 2.4)	.12
HR−/HER2+	2.4 (1.6 to 3.7)	<.0001

NOTE. Top: MVA of covariates associated with PBC-TTBM in subgroup 1. Bottom: hazard ratios of combined HER2/HR categories in predicting MBC-TTBM in subgroup 2. Note that in subgroup 2, individual HER2 and HR categories are not shown due to the significant interaction between HER2 and HR. HER2 status was as previously defined in methods. *P* indicates *Z*-test *P* values.

Abbreviations: HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR, hormone receptor; HR−, HR-negative; HR+, HR-positive; MBC, metastatic breast cancer; MVA, multivariable analysis; PBC, primary breast cancer; TTBM, time to brain metastases; ref, reference.