THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Clinical subtypes in breast cancer patients with brain metastases from an ambispective registry of advanced breast cancer, GEICAM/2014-03 (RegistEM)

Sara López-Tarruella, Ángel Guerrero-Zotano, Silvia Antolín, Josefina Cruz, Purificación Martínez, César A. Rodríguez, Catalina Falo, Álvaro Rodríguez-Lescure, Encarna Adrover, María Hernández, Raquel Andrés, José Ignacio Chacón, José Luis Alonso Romero, Ana Miguel, César Gómez-Raposo, Mireia Margelí, Iria González, Juan Antonio Guerra, Antonio Antón, Ariadna Tibau, Juan José Miralles, María José Escudero, Susana Bezares, Federico Rojo and Isabel Álvarez

Abstract

Background: Breast cancer frequently results in brain metastases (BCBM), leading to poor outcomes. Central nervous system (CNS) involvement entails significant challenges in advanced breast cancer (ABC) patients.

Objectives: To characterize BCBM patients according to surrogate clinical BC subtypes and evaluate the interval between ABC and BCBM detection, both at ABC diagnosis (BCBM1 cohort) and for those who develop BCBM subsequently (BCBM2 cohort). Secondary objectives included analyzing the time-related outcomes by BC subtype.

Design: RegistEM is an ongoing ambispective, observational study of ABC patients diagnosed since January/2016.

Methods: We describe the characteristics of BCBM patients reported by January 22, 2024, categorized by BC subtype on the most recent tumor sample obtained before first-line therapy.

Results: At the cutoff date, 346/1947 (18%) patients diagnosed with ABC between January/2016 and December/2019 developed BCBM, and 288/346 (83%) died. All patients were female, predominantly Caucasian (98%), with a median age of 55 years at ABC diagnosis. The distribution by subtype was 170/346 (49%) HR+/HER2–, 68/346 (20%) HR+/HER2+, 54/346 (16%) HR–/HER2+, and 51/346 (15%) HR–/HER2– (triple negative (TN)). One-fourth (85/346) were in the BCBM1 cohort, with 22/85 (26%) having BCBM as the only metastatic location; in this cohort, median time to BCBM was 38 months, with shorter intervals in HR–/HER2+ and TN subtypes (17 and 18 months, respectively). In the BCBM2 cohort (261/346), the median time to BCBM was 24 months, with the shortest interval in TN (13 months). Median survival from BCBM diagnosis was 26 months (95% confidence interval (CI), 20–35) in BCBM1 and 9 months (95% CI, 7–12) in BCBM2 (hazard ratio, 2.3; 95% CI, 1.7–3.0); TN subtype showed the poorest results (median of 6 months; 95% CI, 3–13).

Conclusion: TN and HER2+ BC subtypes progressed faster to BCBM and had worse outcomes. Survival differed significantly between the two cohorts, BCBM1 and BCBM2. Continued research is essential to improve the treatment and prevention strategies.

Ther Adv Med Oncol

2026, Vol. 18: 1–22

DOI: 10.1177/17588359261421813

Correspondence to:
Sara López-Tarruella
Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Maiquez, 7, Madrid 28009, Spain
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
slopeztarruella@gmail.com

Ángel Guerrero-Zotano
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Fundación Instituto Valenciano de Oncología, Valencia, Spain

Silvia Antolín
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Complejo Hospitalario Universitario A Coruña, Galicia, Spain

Josefina Cruz
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

Purificación Martínez
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Universitario Basurto, Bilbao, Spain

César A. Rodríguez
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
IBSAL, Hospital Universitario de Salamanca, Salamanca, Spain

Catalina Falo
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
ICO Hospitalet, Barcelona, Spain

Álvaro Rodríguez-Lescure
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital General Universitario de Elche, Alicante, Spain
Encarna Adrover
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital General Universitario de Albacete, Albacete, Spain
María Hernández
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Complejo Hospitalario Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain
Raquel Andrés
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
J. Ignacio Chacón
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Universitario de Toledo, Toledo, Spain
José Luis Alonso Romero
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Universitario Virgen de la Arrixaca-IMIB, Murcia, Spain
Ana Miguel
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
ALTHAIA, Xarxa Assistencial de Manresa, Barcelona, Spain
César Gómez-Raposo
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Universitario Infanta Sofía, Madrid, Spain
Mireia Margelí
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
ICO-Badalona, Badalona Applied Research Group in Oncology, Barcelona, Spain
Iria González
GEICAM, Spanish Breast Cancer Group, Madrid, Spain
Hospital Son Llátzer, Palma de Mallorca, Spain
Juan Antonio Guerra
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Plain language summary

How breast cancer subtypes affect brain metastases: results from a Spanish National Registry

Breast cancer can sometimes spread to the brain, leading to serious health problems and shorter survival. This study looked at women with advanced breast cancer (ABC) who developed brain metastases, using information from a large Spanish registry called RegistEM. Researchers studied 346 women who developed brain metastases out of nearly 2,000 patients with ABC diagnosed between 2016 and 2019. They grouped patients based on breast cancer subtype, determined by hormone receptor (HR) and HER2 status. The subtypes were:

- HR+/HER2– (49%)
- HR+/HER2+ (20%)
- HR–/HER2+ (16%)
- Triple negative (HR–/HER2–, 15%)

Patients were also split into two groups:

- BCBM1: Those who already had brain metastases when ABC was diagnosed (25% of cases)
- BCBM2: Those who developed brain metastases later on (75%)

Results showed that triple-negative and HER2-positive cancers spread to the brain more quickly than other types. In the BCBM1 group, the average time until brain metastasis was 38 months overall, but much shorter in triple-negative (18 months) and HER2+ (17 months) cancers. In the BCBM2 group, triple-negative patients developed brain metastases in just 13 months on average. Survival after brain metastasis also varied:

- BCBM1 group: median survival was 26 months
- BCBM2 group: median survival was only 9 months
- Triple-negative patients had the worst outcomes, with a median survival of just 6 months

Conclusion: Certain breast cancer subtypes, especially triple-negative and HER2-positive, are more likely to spread quickly to the brain and lead to poorer survival. Knowing the subtype can help doctors plan better treatment and follow-up strategies. Further research is needed to find ways to delay or prevent brain involvement in these high-risk groups.

Keywords: advanced breast cancer, brain metastases, observational study, real-world evidence, registry

Received: 18 July 2025; revised manuscript accepted: 19 January 2026.

Introduction

Breast cancer is the most common cancer in women globally and, owing to its high incidence, is the second leading cause of brain metastases (BCBM).[1] Central nervous system (CNS) involvement includes both parenchymal and leptomeningeal disease (LMD), with the latter being less common, although it is typically associated with an extremely poor prognosis. Although BCBM are diagnosed across all breast cancer subtypes, LMD occurs disproportionately in invasive lobular carcinoma and triple-negative breast cancer (TN).[2]

A recent systematic review and meta-analysis estimated that BCBM occur in approximately 30% of patients with human epidermal growth factor receptor 2 positive (HER2+) breast cancer or

TN, and 15% of those with hormone receptor (HR)+/HER2− disease.[3] In support of this, autopsy studies have revealed even higher rates, with up to 7.5% of patients with de novo metastatic breast cancer showing CNS involvement. Risk factors for BCBM development include younger age, advanced stage at diagnosis, breast cancer subtype, presence of germline BRCA1/2 mutations, and a history of lung metastases.[1–7]

Despite significant advances in screening and treatment that have reduced breast cancer mortality over the past 40 years in the US,[8] BCBM remain associated with poor prognosis and continue to be a major cause of morbidity and mortality in patients with advanced breast cancer (ABC). Prognosis is influenced by multiple factors, including tumor subtype, performance status (PS), age, and the extent of extracranial disease.[9] The TN and HER2+ subtypes are particularly prone to CNS involvement and often present with more aggressive disease trajectories. LMD, although less common than parenchymal metastases, is associated with poor outcomes. Moreover, the lack of routine CNS screening contributes to delayed diagnosis, which often occurs only after the development of neurological symptoms. Consequently, the quality of life is frequently compromised, and survival remains limited.

Recent advances in systemic therapy have begun to reshape the treatment landscape for BCBM. Novel agents such as antibody–drug conjugates (ADCs), tyrosine kinase inhibitors, and immune checkpoint inhibitors have shown intracranial activity, particularly in HER2+ and TN subtypes.[10] However, effective control of CNS diseases remains complex, and many systemic therapies still exhibit limited blood–brain barrier penetration. A multidisciplinary approach that integrates systemic therapy with local interventions—such as stereotactic radiosurgery or neurosurgical resection—is, therefore, essential to improve outcomes. Regulatory agencies and clinical trials are increasingly including patients with BCBM under predefined eligibility criteria, allowing for a better understanding of treatment efficacy in this population. Moreover, brain metastasis-specific outcomes are now incorporated as key endpoints in some of these trials, highlighting the growing recognition of CNS diseases as critical aspects of breast cancer management. In parallel, growing interest surrounds the role of early detection strategies, including surveillance imaging for asymptomatic patients, particularly those with high-risk subtypes such as HER2+ disease.[11]

Addressing the challenges of BCBM, especially those related to tumor subtype variations, requires a comprehensive understanding of their clinical presentation and management. In this study, we analyzed CNS involvement and clinical outcomes in patients with ABC enrolled in the ongoing GEICAM/2014-03 (RegistEM) registry, focusing on the differences across subtypes.

Materials and methods

Study design

The RegistEM is an ambispective, noninterventional, observational study that includes patients with ABC of any subtype with advanced disease diagnosed from January 2016 onward, including patients who died of any cause (NCT02819882). All patients with incident ABC were included in the registry of each participating institution, unless informed consent was not provided. Treatment decisions were made independent of study participation and were based on local clinical practices.

This study was sponsored and managed by the GEICAM Spanish Breast Cancer Research Group, and its database is ongoing. The data were gathered in an electronic case report form by a specialized clinical research assistant from the Medical Oncology Department directly from the medical records. The GEICAM staff monitors and validates the data quality of all datasets by submitting queries to the investigators if deemed necessary.

Follow-ups included periodic updates during the course of metastatic disease at the time of progressive disease (PD) or changes in the treatment regimen. Each patient is intended to undergo a follow-up of at least 5 years, unless any contraindications prevent this study period, or until death. Thirty-eight institutions from 15 Autonomic Communities participated in this study to provide a diverse overview of the ABC landscape in Spain. The study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the institutional review boards (IRBs) of the participating sites according to the applicable legislation. Written informed consent was obtained

Hospital Universitario de Fuenlabrada, Madrid, Spain

Antonio Antón
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Hospital Universitario Miguel Servet, Instituto de Investigación Sanitaria de Aragón, Universidad de Zaragoza, Zaragoza, Spain

Ariadna Tibau
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Juan José Miralles
María José Escudero
Susana Bezares
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Federico Rojo
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII, Madrid, Spain

Isabel Álvarez
GEICAM, Spanish Breast Cancer Group, Madrid, Spain

Unidad de Gestión del Cáncer de Guipúzcoa, Osakidetza-OSI Donostialdea-Onkologikoa-BioDonostia, San Sebastián, Spain

from all patients, although exceptions were authorized by the IRBs for patients who died.

Breast cancer surrogate clinical subtypes were assessed on the most recent tumor lesion (distant metastasis, and if not available, primary breast tumor) and defined as HR+ (⩾1%)/HER2−, HR+/HER2+, HR−/HER2+, and TN. Cases in which the BC subtype changed between the primary tumor and distant metastases were classified as "phenotype conversion." Primary and secondary endocrine therapy (ET) resistance classification was made according to the international consensus guidelines for ABC management (ABC 5).[12] The potential impact of incorporating new drugs into the therapeutic armamentarium for ABC has been evaluated in patients who received these drugs before the diagnosis of BCBM. This study adhered to the established EQUATOR guidelines with particular attention to the recommendations for Observational Studies in Epidemiology (STROBE)[13] (Supplemental Material).

Objectives of the current analysis

The main objective was to describe the characteristics of patients with BCBM diagnosed up to the cutoff date established for the analysis, according to the surrogate clinical BC subtypes determined by immunohistochemistry, with or without in situ hybridization, on metastatic tumor tissue before first-line therapy and, in the absence of metastatic tissue, on the primary breast tumor. In addition, to better understand the timing of CNS involvement, the patients were categorized into those with BCBM at ABC diagnosis (BCBM1 cohort) and those who developed BCBM subsequently (BCBM2 cohort). Secondary objectives included the description of time-related outcomes by BC subtype, such as the time interval from primary BC diagnosis to BCBM for the BCBM1 cohort, the time interval from ABC diagnosis to BCBM for the BCBM2 cohort, and survival from BCBM diagnosis in all patients. Exploratory analyses were also conducted to characterize the type of ET resistance in the HR+/HER2− population with BCBM from both BCBM1 and BCBM2 cohorts as well as to evaluate the potential impact of new drugs on the outcomes of HR+/HER2− and HER2+ (regardless of HR expression) populations.

Eligibility criteria

The RegistEM study included adult women and men diagnosed with ABC from January 2016 onward. ABC included unresectable locally advanced or metastatic cases, either after disease recurrence or as de novo metastatic disease. In the current analysis, patients diagnosed with ABC between January 2016 and December 2019 who developed BCBM on January 22, 2024, were included.

In addition, patients had to meet the following criteria for study entry: age 18 years or older; availability and willingness to provide written informed consent (although patients who had died were also allowed to be included in the study); accessibility to medical records; and availability of all data related to disease management.

Statistical considerations

Continuous variables are reported as the number of missing data points, mean, standard deviation, median, range, and interquartile range (IQR). Categorical variables are expressed as frequencies and numbers of missing values and compared using the Chi-square (χ^2) test or Fisher's exact test, as appropriate. The proportion of patients with BCBM was calculated for the entire study population and surrogate clinical BC subtypes.

Survival from BCBM diagnosis was calculated as the time from BCBM diagnosis to death from any cause or last contact. Time-to-event curves were estimated using the Kaplan–Meier method and compared using the log-rank or Wilcoxon test, as appropriate, based on the distribution. Multivariate Cox regression analyses were used to assess factors associated with survival from BCBM diagnosis, incorporating covariates based on clinical relevance and univariate analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to estimate relative risk. Proportional hazard assumptions were tested using cumulative Martingale residuals. All tests used a two-sided alpha value of 0.05. Statistical analyses were conducted using SAS® software (version 7.1; SAS Institute Inc., Cary, NC, USA). No imputation of missing data was performed.

Results

A total of 1947 patients were included in the RegistEM study based on the cutoff date for this analysis. After a median follow-up of 37 months (IQR 20–56 months), BCBM were identified in 346 (18%) patients. Of these, 85 (25%) patients presented with BCBM at ABC diagnosis (BCBM1

cohort), and 261 (75%) developed BCBM during the course of their disease (BCBM2 cohort). The main clinicopathological characteristics of the patients are presented in Tables 1 and 2.

Regarding surrogate clinical breast cancer subtypes on patients with BCBM ($n=346$), the most frequent subtype was HR+/HER2− ($n=170$, 49%), followed by HR+/HER2+ ($n=68$, 20%), HR−/HER2+ ($n=54$, 16%), and TN ($n=51$, 15%). When considering all patients enrolled on the RegistEM study by the cutoff date for the current analysis ($n=1947$), HER2+ tumors (both HR+ and HR−) had the highest proportions of BCBM. The distribution by breast cancer subtype in patients with BCBM was 45% (54/121) in HR−/HER2+, 31% (68/222) in HR+/HER2+, 25% (51/201) in TN, and 13% (170/1307) in HR+/HER2− tumors (χ^2 test, $p<0.001$). The subtype was unknown in three patients with BCBM.

Among patients with recurrent early-stage breast cancer (EBC), the median time to ABC diagnosis was 49 months (IQR 24–100). This interval was shorter in patients with TN (median, 20 months). Notably, 57% of these cases occurred within 12–24 months of EBC diagnosis. In the BCBM2 cohort (development of BCBM after ABC diagnosis), the time from ABC to BCBM onset was generally shorter in patients with recurrent EBC than in those with ABC. This difference was observed across all subtypes: HR+/HER2− (26 (IQR 16–42) vs 39 (IQR 24–48) months), HR+/HER2+ (17 (IQR 11–37) vs 33 (IQR 21–40) months), HR−/HER2+ (15 (IQR 10–24) vs 22 (IQR 15–32) months), and TN (11 (IQR 9–29) vs 13 (IQR 8–24) months), with the smallest difference seen in patients with TN (Kruskal–Wallis test, $p=0.0516$).

In the BCBM2 cohort, both the timing and cumulative incidence (CuIn) of brain metastases varied according to breast cancer subtype (Table 3, Figure 1). At 2 years, CuIn was lowest in HR+/HER2− tumors (4.09%) and highest in HER2+ (12.08% HR+, 24.77% HR−) and TN (11.73%) tumors. While BCBM in patients with the HR+/HER2− subtype mostly occurred beyond 24 months, HER2+ and TN showed an earlier onset, with a peak at approximately 36 months. These patterns reflect distinct CNS tropism across subtypes.

At the time of ABC diagnosis, visceral involvement was present in over 80% of patients across all breast cancer subtypes, except for the HR+/HER2− group, where the rate was lower (65%; χ^2 test; $p<0.001$). As detailed in Table 1, 22 of 346 patients with BCBM (6%) had CNS involvement as the only metastatic location at ABC diagnosis, with no significant differences observed between the subtypes.

The CNS involvement was parenchymal in 277 of 346 patients (80%), with the following subtype-specific frequencies: HR+/HER2− 123/170 (72%), HR+/HER2+ 60/68 (88%), HR−/HER2+ 51/54 (94%), and TN, 41/51 (80%). LMD alone was observed in 37 patients (11%): 28/170 (17%) in HR+/HER2−, 1/68 (2%) in HR+/HER2+, 1/54 (2%) in HR−/HER2+, 6/51 (12%) in TN, and 1 patient had the subtype unknown. Both parenchymal and leptomeningeal involvement occurred in 24 patients (7%): 13/170 (8%) HR+/HER2−, 6/68 (9%) HR+/HER2+, 2/54 (4%) HR−/HER2+, and 3/51 (6%) TN. In eight patients (2%), the pattern of CNS involvement was not specified.

Two or more brain lesions were reported in approximately 57% of patients, with the highest proportion in the HR+/HER2+ group (65%). A single brain lesion was observed in 34% of patients with the HR+/HER2− subtype (57/170), 31% of those with HR+/HER2+ (21/68), 41% of those with HR−/HER2+ (22/54), and 35% of those with TN (18/51). Among patients with LMD ($n=61$), the initial CNS lesion was identified by magnetic resonance imaging in 40 cases (66%), computed tomography in 19 cases (31%), cerebrospinal fluid (CSF) analysis in 1 case, and was unknown in 1 patient.

When considering all patients with BCBM ($n=346$), the proportion diagnosed with CNS involvement at ABC diagnosis was similar across HR+/HER2−, HR+/HER2+, and HR−/HER2+ subtypes (around 22%), but notably higher in patients with TN (43%; χ^2, $p=0.01$). In the BCBM1 cohort, 22/85 (26%) patients had CNS involvement as the only site of metastasis. Subtype-specific frequencies were HR+/HER2− 9 (41%), HR+/HER2+ 3 (14%), HR−/HER2+ 6 (27%), and TN 4 (18%). A sensitivity analysis was performed on BCBM1 patients adjusting for extracranial disease burden, and survival from BCBM was found to be longer in patients without visceral disease, although the difference was not statistically different (Supplemental Material). Detailed characteristics of both BCBM1 and BCBM2 cohorts are outlined in Tables 2 and 4.

Table 1. Characteristics of patients with BCBM by surrogate BC clinical subtype.

Patient characteristics	HR+ HER2−	HR+ HER2+	HR− HER2+	TN	Total
	n = 170 (49%)	*n* = 68 (20%)	*n* = 54 (16%)	*n* = 51 (15%)	*n* = 346[a]
Characteristics at first BC diagnosis					
Extension of disease, *n* (%)					
EBC	127 (75)	40 (59)	32 (59)	37 (72)	238 (69)[b]
De novo metastatic BC	43 (25)	28 (41)	22 (41)	13 (26)	107 (31)
ULABC	0	0	0	1 (2)	1 (0.3)
Age at first BC diagnosis (years)					
Median (IQR)	50 (43–58)	51 (42–56)	55 (47–68)	54 (45–62)	51 (44–60)
Menopausal status at EBC diagnosis, *n* (%)					
Postmenopausal	53 (42)	15 (38)	15 (47)	21 (57)	105 (44)
Premenopausal	74 (58)	25 (62)	17 (53)	16 (43)	133 (56)
Stage at diagnosis of patients with EBC or ULABC, *n* (%)					
I	12 (9)	4 (10)	2 (6)	4 (11)	22 (9)
II	76 (60)	19 (48)	15 (47)	25 (66)	136 (57)
III	26 (20)	16 (40)	12 (38)	8 (21)	63 (26)
Unknown	13 (10)	1 (2)	3 (9)	1 (3)	18 (8)
Morphological tumor type, *n* (%)					
Ductal	140 (83)	55 (86)	50 (94)	44 (88)	292 (86)
Lobular	20 (12)	6 (9)	2 (4)	4 (8)	32 (10)
Other	8 (5)	3 (5)	1 (2)	2 (4)	14 (4)
Histological grade, *n* (%)					
1	8 (5)	2 (3)	3 (6)	1 (2)	14 (4)
2	73 (43)	18 (27)	19 (35)	11 (22)	122 (35)
3	58 (34)	35 (52)	19 (35)	31 (61)	144 (42)
Unknown	31 (18)	13 (19)	13 (24)	8 (16)	66 (19)
Previous treatment for EBC, *n* (%)					
Neoadjuvant	5 (4)	3 (8)	4 (13)	10 (26)	23 (10)
Adjuvant	78 (61)	19 (48)	13 (41)	18 (47)	129 (54)
Neoadjuvant and adjuvant	41 (32)	17 (43)	15 (47)	7 (18)	80 (34)
Unknown	3 (2)	1 (3)	0	3 (8)	7 (3)
Time to ABC from EBC diagnosis, *n* (%)					
⩽1 year	9 (7)	3 (8)	2 (6)	0	14 (6)
>1 to ⩽3 years	28 (22)	10 (25)	12 (38)	25 (68)	76 (32)

(Continued)

Table 1. (Continued)

Patient characteristics	HR+ HER2–	HR+ HER2+	HR– HER2+	TN	Total
	n **= 170 (49%)**	***n*** **= 68 (20%)**	***n*** **= 54 (16%)**	***n*** **= 51 (15%)**	***n*** **= 346**[a]
>3 to ⩽5 years	35 (28)	13 (33)	9 (28)	7 (19)	64 (27)
>5 to ⩽9 years	33 (26)	6 (15)	4 (13)	4 (11)	47 (20)
>9 years	22 (17)	8 (20)	5 (16)	1 (3)	37 (16)
Median (IQR)	64 (29–106)	48 (30–109)	45 (18–75)	20 (17–42)	49 (24–100)
Demographic and tumor characteristics at ABC diagnosis					
Age at ABC diagnosis (years)					
Median (range)	54 (46–66)	53 (45–60)	59 (51–69)	56 (49–64)	55 (47–65)
Menopausal status at ABC diagnosis, *n* (%)					
Postmenopausal	107 (63)	40 (59)	37 (69)	35 (69)	221 (64)
Premenopausal	63 (37)	28 (41)	16 (30)	16 (31)	124 (36)
Morphological type in patients with de novo metastatic disease, *n* (%)					
Ductal	34 (79)	18 (64)	20 (91)	9 (69)	82 (77)
Lobular	8 (19)	5 (18)	1 (5)	2 (15)	16 (15)
Other	1 (2)	2 (7)	0	1 (8)	4 (4)
Histological grade in patients with de novo metastatic disease, *n* (%)					
1	3 (7)	0	0	0	3 (3)
2	18 (42)	9 (32)	10 (46)	1 (8)	38 (36)
3	16 (37)	13 (46)	9 (41)	9 (69)	48 (45)
Unknown	6 (14)	6 (21)	3 (14)	3 (23)	18 (17)
Type of organs involved, *n* (%)					
Visceral	110 (65)	57 (84)	47 (87)	44 (86)	260 (75)
Bone without visceral involvement	58 (34)	10 (15)	4 (7)	1 (2)	74 (21)
Soft tissue only	2 (1)	1 (2)	3 (6)	6 (12)	12 (4)
More frequent metastatic locations at ABC diagnosis, *n* (%)					
Bone	116 (68)	42 (62)	19 (35)	14 (28)	194 (56)
Lymph nodes	74 (44)	35 (52)	30 (56)	29 (57)	169 (49)
Liver	45 (27)	27 (40)	16 (30)	8 (16)	97 (28)
Lung	55 (32)	24 (35)	26 (48)	31 (61)	138 (40)
Pleura	17 (10)	4 (6)	9 (17)	4 (8)	34 (10)
Peritoneum	7 (4)	2 (3)	1 (2)	2 (4)	12 (4)
Brain	35 (21)	15 (22)	12 (22)	22 (43)	85 (25)
Number of metastatic locations, *n* (%)					
Only 1	52 (31)	13 (19)	11 (20)	8 (16)	85 (25)
⩾2	118 (69)	55 (81)	43 (80)	43 (84)	261 (75)

[a]Three patients had subtype unknown.
[b]Thirty patients were clinical subtype-converted.
ABC, advanced breast cancer; BC, breast cancer; BCBM, brain metastases due to breast cancer; EBC, early-stage breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; TN, triple negative; ULABC, unresectable locally advanced breast cancer.

Table 2. Characteristics of patients according to the time of BCBM diagnosis in the ABC setting.

Patient characteristics	BM at ABC diagnosis (BCBM1)	BM after ABC diagnosis (BCBM2)
	n **= 85 (25%)**	***n*** **= 261 (75%)**
Characteristics at BC diagnosis		
Extension of disease, *n* (%)		
Early-stage BC	68 (80)	170 (65)
De novo metastatic ABC	17 (20)	90 (35)
ULABC	0	1 (<1)
Age at BC diagnosis, years		
Median (range)	54 (45–64)	51 (44–58)
cT in patients with neoadjuvant therapy, *n* (%[a])		
	n = 31 (missing *n* = 1)	*n* = 72 (missing *n* = 1)
T1c	6 (20)	8 (11)
T2	18 (60)	42 (59)
T3	2 (7)	12 (17)
T4	4 (13)	9 (13)
Clinical lymph node status in patients with neoadjuvant therapy, *n* (%[a])		
	n = 31 (missing *n* = 3)	*n* = 72 (missing *n* = 9)
N0	7 (25)	6 (10)
N1	13 (46)	43 (68)
N2	2 (7)	7 (11)
N3	5 (18)	4 (6)
NX	1 (4)	3 (5)
Pathological tumor size in patients with adjuvant therapy, *n* (%[a])		
	n = 33 (missing *n* = 3)	*n* = 96 (missing *n* = 5)
T1	11 (37)	42 (46)
T2	18 (60)	45 (50)
T3	1 (3)	2 (2)
T4	0	2 (2)
Pathological lymph node status in patients with adjuvant therapy, *n* (%[a])		
	n = 33 (missing *n* = 4)	*n* = 96 (missing *n* = 11)
N0	11 (38)	29 (34)

(Continued)

Table 2. (Continued)

Patient characteristics	BM at ABC diagnosis (BCBM1)	BM after ABC diagnosis (BCBM2)
	***n* = 85 (25%)**	***n* = 261 (75%)**
N1	15 (52)	39 (46)
N2	1 (3)	6 (7)
N3a	2 (7)	11 (13)
Stage at diagnosis in early-stage BC patients, *n* (%)		
I	4 (6)	18 (11)
II	45 (66)	91 (53)
III	14 (21)	49 (29)
Unknown	5 (7)	13 (8)
Previous radiation therapy for early-stage BC, *n* (%)		
	53/68 (78)	127/171 (74)
Type of breast and regional lymph nodes surgery at early-stage BC, *n* (%[a])		
	n = 68 (missing *n* = 0)	*n* = 171 (missing *n* = 6)
Breast surgery at early-stage BC		
Breast conservative surgery	33 (49)	63 (38)
Breast conservative surgery + mastectomy	3 (4)	8 (5)
Mastectomy	32 (47)	94 (57)
Lymph nodes surgery at early-stage BC		
SLNB	19 (28)	32 (19)
ALND	26 (38)	92 (54)
SLNB + ALND	14 (21)	23 (14)
Histological grade, *n* (%)		
	n = 85	*n* = 261
1	4 (5)	10 (4)
2	25 (29)	97 (37)
3	43 (51)	101 (39)
X	13 (15)	53 (20)
Previous treatment for patients with early-stage BC, *n* (%)		
Neoadjuvant	9 (13)	14 (8)
Adjuvant	33 (49)	96 (56)
Neoadjuvant and adjuvant	22 (32)	58 (34)
Unknown	4 (6)	3 (2)

(Continued)

Table 2. (Continued)

Patient characteristics	BM at ABC diagnosis (BCBM1)	BM after ABC diagnosis (BCBM2)
	n **= 85 (25%)**	***n*** **= 261 (75%)**
Time to ABC from early-stage BC diagnosis, *n* (%)		
⩽1 year	6 (9)	8 (5)
>1 to ⩽3 years	28 (41)	48 (28)
>3 to ⩽5 years	12 (18)	52 (31)
>5 to ⩽9 years	12 (18)	35 (21)
>9 years	10 (15)	27 (16)
Median (IQR), mo	36 (16–89)	52 (27–101)
Demographic and tumor characteristics at ABC diagnosis		
Age at ABC diagnosis, years		
Median (range)	59 (47–68)	54 (47–64)
Menopausal status at ABC diagnosis, *n* (%)		
Postmenopausal	56 (66)	165 (63)
Premenopausal	29 (34)	95 (36)
NA	0	1 (<1)
BC clinical subtype, *n* (%)		
HR+ HER2−	35 (41)	135 (52)
HR+ HER2+	15 (18)	53 (20)
HER2+	12 (14)	42 (16)
TN	22 (26)	29 (11)
Unknown	1 (1)	2 (1)
More frequent metastatic locations at ABC diagnosis, *n* (%)		
Bone	30 (35)	164 (63)
Lymph node	31 (37)	138 (53)
Liver	17 (20)	80 (31)
Lung	33 (39)	105 (40)
Soft tissue	8 (9)	15 (6)
Pleura	7 (8)	27 (10)
Brain	85 (100)	0
Only CNS metastases	22 (26)	0
Number of metastatic locations, *n* (%)		
Only one	22 (26)	63 (24)
⩾2	63 (74)	198 (76)

[a]The percentages for each variable were calculated excluding missing data.
ABC, advanced breast cancer; ALND, axillary lymph node dissection; BC, breast cancer; BCBM, breast cancer with brain metastases; BCBM1, brain metastases at advanced breast cancer diagnosis; BCBM2, brain metastases after advanced breast cancer diagnosis; BM, brain metastases; CNS, central nervous system; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; NA, not available; SLNB, sentinel lymph node biopsy; TN, triple negative; ULABC, unresectable locally advanced breast cancer.

Table 3. Culn of BCBM from ABC diagnosis in the BCBM2 cohort, among the 1767 patients without BCBM at ABC diagnosis.

Time from ABC to BCBM	HR+/HER2− (*N* = 1272)				HR+/HER2+ (*N* = 207)				HR−/HER2+ (*N* = 109)				TN (*N* = 179)			
	Culn	Non-Culn	%	95% CI	Culn	Non-Culn	%	95% CI	Culn	Non-Culn	%	95% CI	Culn	Non-Culn	%	95% CI
⩽6 months	10	10	0.79	0.3–1.3	2	2	0.97	0.1–3.7	4	4	3.67	1–9.4	3	3	1.68	0.4–5
12 months	24	14	1.89	1.1–2.6	11	9	5.31	2.3–8.4	11	7	10.09	4.4–15.8	14	11	7.82	3.9–11.8
24 months	52	28	4.09	3–5.2	25	14	12.08	7.6–16.5	27	16	24.77	16.7–32.9	21	8	11.73	7–16.5
36 months	81	29	6.37	5–7.7	38	13	18.36	13.1–23.6	37	10	33.94	25.1–42.8	29	8	16.20	10.8–21.6
60 months	126	45	9.91	8.3–11.6	48	10	23.19	17.4–28.9	39	2	35.78	26.8–44.8	29	0	16.20	10.8–21.6
>60 months	134	8	10.53	8.9–12.2	53	5	25.60	19.7–31.6	42	3	38.53	29.4–47.7	29	0	16.20	10.8–21.6

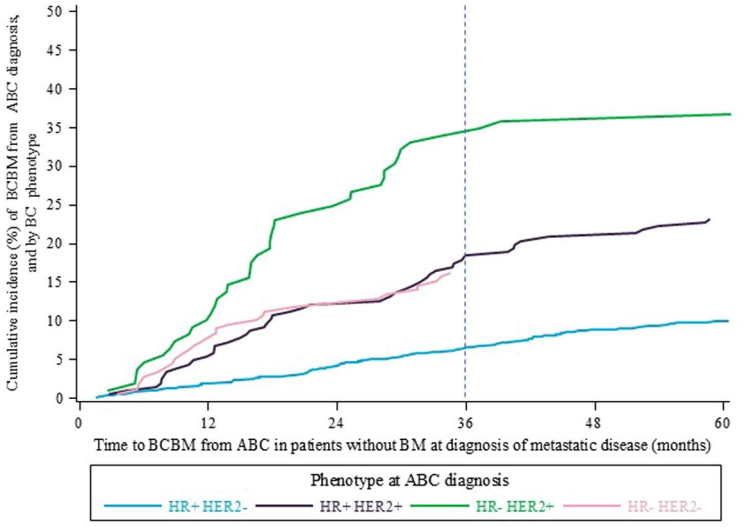
ABC, advanced breast cancer; BC, breast cancer; BCBM, breast cancer with brain metastases; BCBM2, brain metastases after advanced breast cancer diagnosis; BM, brain metastases; Culn, cumulative incidence; HER2, human epidermal growth factor receptor; HR, hormone receptor.

Based on the cutoff date for this analysis and after a median follow-up of 35 months for the BCBM population, death was reported in 288/346 (83%) patients, 14 (4%) were lost to follow-up, and PD was the primary cause of death in 246/288 (85%) patients.

The median survival from BCBM diagnosis differed significantly between the cohorts: 26 months (95% CI, 20–35) in the BCBM1 cohort ($n = 85$) versus 9 months (95% CI, 7–12) in the BCBM2 cohort ($n = 261$; Figure 2). Statistically significant differences were also observed across BC subtypes ($p < 0.001$): Patients with TN had a median survival of 6 months (95% CI, 3−13), HR+/HER2− of 9 months (95% CI, 6−13), HR+/HER2+ of 21 months (95% CI, 17−29), and HR−/HER2+ of 23 months (95% CI, 14−26; Figure 3). In addition, the analysis of each subtype comparing BCBM1 and BCBM2 cohorts showed statistically significant differences in HR+/HER2− and HR−/HER2+ subtypes ($p < 0.001$ and $p = 0.012$, respectively; Figure 4(a)–(d)). Furthermore, survival varied based on the pattern of CNS involvement: patients with LMD plus parenchymal disease had a median survival of 14 months (95% CI, 3−28), those with isolated LMD had 4 months (95% CI, 2−11), and those with isolated parenchymal metastases had 15 months (95% CI, 10−18; Wilcoxon test; $p = 0.001$).

In the multivariate Cox regression analysis, several factors were independently associated with worse survival following BCBM diagnosis. These included BCBM development during the course of advanced disease (BCBM2 cohort) versus at the time of ABC diagnosis (BCBM1 cohort; HR, 2.6; 95% CI, 1.9−3.6); the presence of two or more CNS lesions compared to a single lesion (HR, 1.6; 95% CI, 1.2−2.1); age (HR, 1.015; 95% CI, 1.01−1.03); and HER2− status compared to HER2+ disease (HR, 2.3; 95% CI, 1.8−3.1). The results of the univariate and multivariate Cox regression analyses are presented in Table 5.

We aimed to characterize patterns of endocrine resistance in the subgroup of patients with HR+/HER2− BCBM. Among all patients with the HR+/HER2− subtype included in the RegistEM study, 1180 (90%) exhibited endocrine resistance, with 286 (22%) having primary resistance and 894 (68%) secondary resistance, according to the 5th international consensus guidelines for



Abbreviations: ABC: advanced breast cancer; BCBM: breast cancer with brain metastases; HER2: human epidermal growth factor receptor 2; HR: hormone receptor.

Figure 1. Cumulative incidence of BCBM from ABC diagnosis by surrogate BC clinical subtype in patients without BCBM at diagnosis of ABC ($n = 1272$).
ABC, advanced breast cancer; BC, breast cancer; BCBM, breast cancer with brain metastasis.

the management of ABC. Among patients with the HR+/HER2− subtype ($n = 170$), primary endocrine resistance was identified in 54 (32%) patients, while secondary endocrine resistance was observed in 112 (66%) patients.

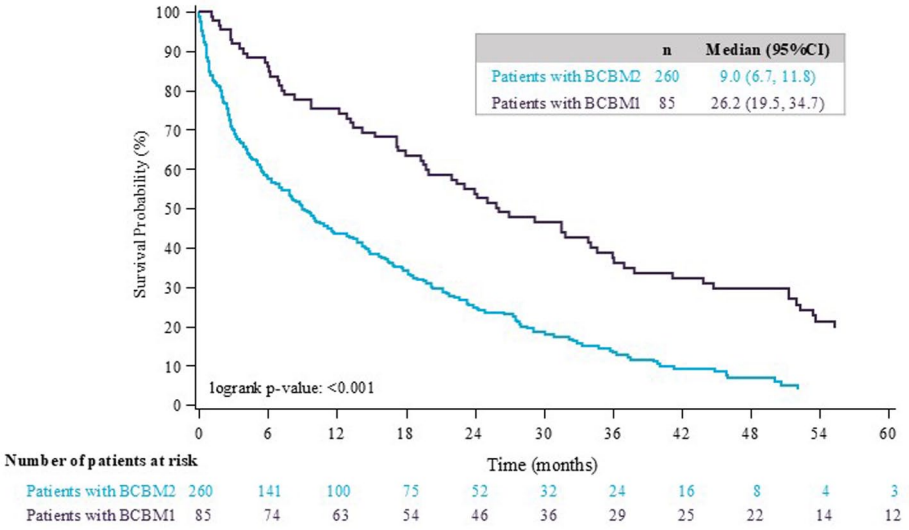
In the BCBM1 cohort ($n = 35$), primary and secondary endocrine resistance were identified in 9 (26%) and 25 (71%) patients, respectively, whereas in the BCBM2 cohort ($n = 135$), these were observed in 45 (33%) and 87 (64%) patients, respectively. The median time to BCBM from ABC diagnosis for the BCBM2 cohort was 22 months (IQR, 11–35) for patients with primary endocrine resistance and 36 months (IQR, 22–47) for those with secondary endocrine resistance. There were no statistically significant differences in survival after BCBM diagnosis based on the pattern of endocrine resistance (Wilcoxon test; $p = 0.146$). The median survival from BCBM diagnosis was 6 months (95% CI, 3–12) for patients with primary endocrine resistance and 11 months (95% CI, 7–17) for patients with secondary endocrine resistance (Figure 5).

Among 135/261 (52%) patients with the HR+/HER2− subtype in the BCBM2 cohort, 92 (68%) received CDK4/6 and/or PI3K signaling pathway inhibitors prior to their BCBM diagnosis. The median time from ABC to BCBM diagnosis was significantly longer in patients who received these targeted therapies, 16 months ($Q1–Q3$, 7–30) compared to 36 months ($Q1–Q3$, 23–46; Kruskal–Wallis test; $p < 0.001$). Two sensitivity analyses were conducted using patients treated with CDK4/6 and mTOR inhibitors before the diagnosis of BCBM. In both analyses, patients who received these treatments had a longer interval between ABC and BCBM diagnoses. Additional analyses are required to confirm these findings. The proportion of patients treated with PIK3CA and PARP inhibitors was 4% and 2%, respectively; therefore, no further analyses were conducted for these groups. In the HER2+ BCBM2 subgroup, 27 patients (28%) were treated with newer anti-HER2 agents (afatinib, T-DM1, trastuzumab, deruxtecan, tucatinib, or neratinib) before BCBM development, whereas 65 patients (68%) received other anti-HER2 drugs (trastuzumab, trastuzumab plus pertuzumab, or lapatinib). The median time from ABC to BCBM diagnosis was 30 months ($Q1–Q3$, 16–40 months) in patients treated with newer anti-HER2 agents, compared to 18 months (95% CI, 11–32 months) in patients receiving conventional anti-HER2 therapies (Kruskal–Wallis test; $p = 0.0664$). Only three patients with TN in the BCBM2 cohort received immune checkpoint inhibitors prior to BCBM diagnosis, and no further analysis was conducted owing to the limited sample size.

Table 4. Metastatic disease burden in patients with BCBM at ABC diagnosis (BCBM1) and after ABC diagnosis (BCBM2) by breast cancer clinical subtype.

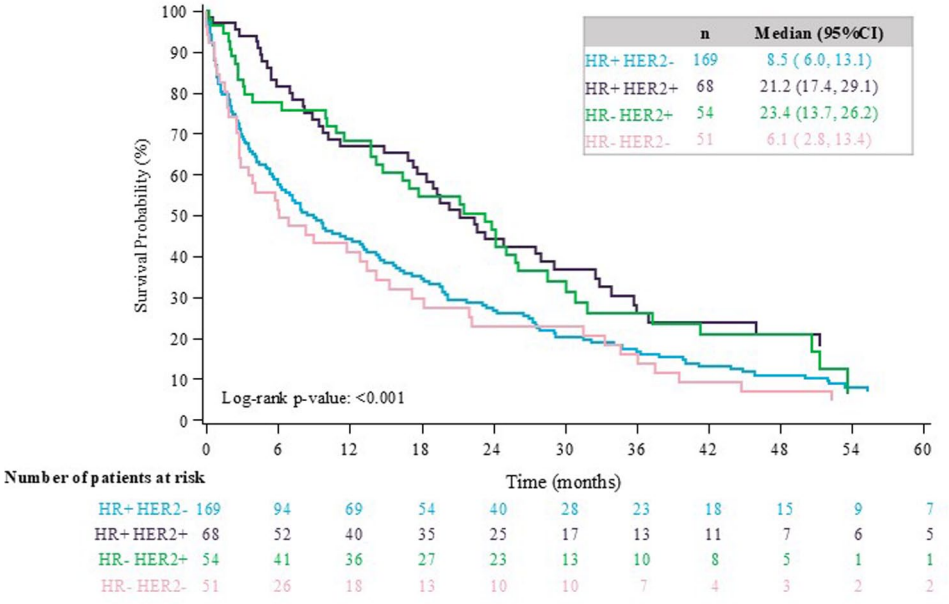
Patient characteristics	HR+/HER2−		HR+/HER2+		HR−/HER2+		HR−/HER2−	
	BCBM1	BCBM2	BCBM1	BCBM2	BCBM1	BCBM2	BCBM1	BCBM2
N	**35**	**135**	**15**	**53**	**12**	**42**	**22**	**29**
Extension of disease, *n* (%)								
Early-stage BC, *n*	24 (69)	103 (76)	12 (80)	28 (53)	10 (83)	22 (52)	22 (100)	15 (52)
De novo metastatic BC, *n*	11 (31)	32 (24)	3 (20)	25 (47)	2 (17)	20 (48)	0	14 (48)
Type of CNS involvement at BCBM diagnosis, *n* (%[a])								
Leptomeningeal	2 (6)	26 (19)	1 (7)	0	0	1 (2)	2 (9)	4 (14)
Leptomeningeal + Parenchymal	1 (3)	12 (9)	0	6 (11)	1 (8)	1 (2)	1 (5)	2 (7)
Only CNS	2 (6)	4 (3)	0	1 (2)	0	0	0	1 (3)
Parenchymal	30 (86)	93 (69)	14 (93)	46 (87)	11 (92)	40 (95)	19 (86)	22 (76)
Location of metastatic lesions at ABC diagnosis, *n* (%)								
Brain	35	0	15	0	12	0	22	0
Bone	14 (40)	102 (76)	5 (33)	37 (70)	1 (8)	18 (43)	9 (41)	5 (17)
Lymph nodes	14 (40)	60 (44)	6 (40)	29 (55)	3 (25)	27 (64)	7 (32)	22 (76)
Liver	9 (26)	36 (27)	2 (13)	25 (47)	1 (8)	15 (36)	4 (18)	4 (14)
Lung	10 (29)	45 (33)	5 (33)	19 (36)	4 (33)	22 (52)	13 (59)	18 (62)
Soft tissue	5 (14)	6 (4)	0	2 (4)	0	5 (12)	3 (14)	2 (7)
Pleura	4 (11)	13 (10)	0	4 (8)	2 (17)	7 (17)	1 (5)	3 (10)
Peritoneum	3 (9)	4 (3)	0	2 (4)	0	1 (2)	0	2 (7)
Time to ABC (patients with early-stage BC) months, %								
Median	68	63	69	46	17	52	18	23
IQR months	27–117	29–102	19–123	32–75	15–56	26–80	16–68	19–42
Time to BCBM from ABC months, %								
Median		30		29		18		13
IQR months		17–43		13–40		12–28		9–24
Survival from BCBM diagnosis (months), median (95% CI)	34	6	23	21	32	16	13	3
	(20–54)	(4–8)	(7–51)	(11–28)	(24–54)	(10–23)	(6–22)	(2–12)

[a]In 36 (10%) patients, the CNS involvement was only leptomeningeal.
ABC, advanced breast cancer; BC, breast cancer; BCBM, breast cancer with brain metastases; BCBM1, brain metastases at advanced breast cancer diagnosis; BCBM2, brain metastases after advanced breast cancer diagnosis; CI, confidence interval; CNS, central nervous system; HER2, human epidermal growth factor receptor; HR, hormone receptor; IQR, interquartile range; mo., months.



Abbreviations: BCBM: breast cancer with brain metastases; BCBM1: brain metastases at advanced breast cancer diagnosis; BCBM2: brain metastases after advanced breast cancer diagnosis .

Figure 2. Survival from BCBM diagnosis by temporal pattern of BCBM diagnosis.
BCBM, breast cancer with brain metastases; BCBM1, brain metastases at advanced breast cancer diagnosis; BCBM2, brain metastases after advanced breast cancer diagnosis.



Abbreviations: HER2: human epidermal growth factor receptor; HR: hormone receptor.

Figure 3. Survival from BCBM diagnosis by subtype.
BCBM, breast cancer with brain metastases; HER2, human epidermal growth factor receptor; HR, hormone receptor.

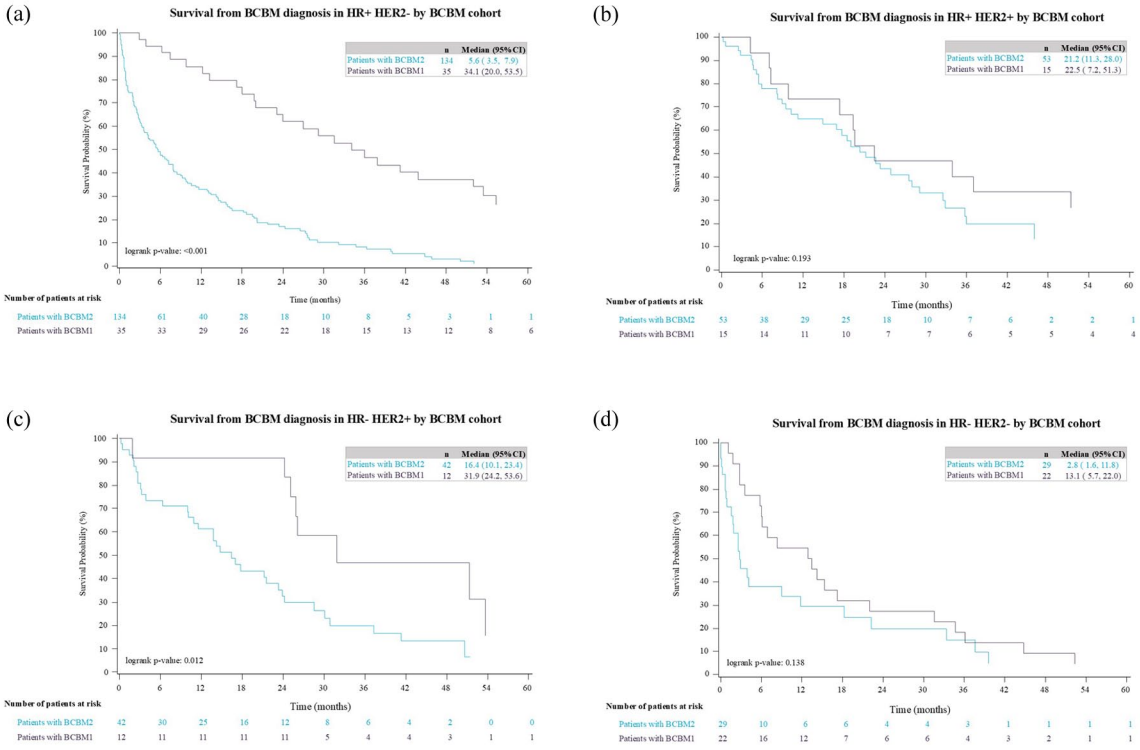


Figure 4. (a–d) Survival from BCBM diagnosis by subtype and BCBM cohort.
BCBM, breast cancer with brain metastases.

Discussion

CNS recurrence of breast cancer is a major cause of patient morbidity and remains a major challenge in the ABC setting.[14] Improving the treatment strategies requires a thorough understanding of biology, clinical features, treatment modalities, and expected outcomes. Our study draws insights from the GEICAM/2014-03 (RegistEM) database, offering contemporary data on ABC across all subtypes. This dataset, together with previously published evidence,[1,3,11,15–20] may inform future clinical trial designs aimed at improving outcomes in patients with BCBM.

In our registry, the incidence is 18%, similar to that reported in the U.S.A. Flatiron cohort, which included more than 18,000 patients: 6% had BCBM at the index date and 13% developed incident BCBM during follow-up.[20] Breast cancer developed de novo metastatic disease in one-third of our patients, and 25% presented with BCBM at ABC diagnosis, similar to the ESME dataset.[17,21] Among BCBM patients in our registry, the HR+/HER2− subtype predominated (49%), HR+/HER2+, HR−/HER2+, and TN accounted for 20%, 16%, and 15% of cases, respectively. These trends aligned with the ESME dataset[22] and captured the changing subtype distributions observed in the retrospective German BCBM registry from 2000 to 2016.[18] Notably, among patients with the HER2+ subtype, regardless of HR status, 36% developed BCBM over a longer follow-up period in our registry, which is similar to the 31% reported in the US-SystHER2 cohort study.[19] In the RegistEM population, patients with HR−/HER2+ breast cancer had the highest BCBM incidence, while those with the HR+/HER2− subtype had the lowest rate (13%), consistent with the recent real-world U.S.A.-Flatiron dataset.[20] Regarding BCBM diagnosis in Spain, it is important to mention that the latest update of the SEOM–GEICAM–SOLTI clinical guidelines[23] from 2022 was the first national consensus, aligned with previous ESMO guidelines[24]; while CNS screening in asymptomatic patients is not routinely recommended, it might be considered in patients at a higher risk (HER2+ and TN) if its detection may influence treatment decisions.[25] The impact of this pragmatic approach will merit further attention in parallel with ongoing prospective clinical trials (NCT04030507) in the near future. Although the RegistEM study

Table 5. Univariate and multivariate Cox regression analyses for survival from BCBM diagnosis.

Parameter	Univariate analysis				Multivariate analysis[a] ($n = 345$)	
	N	Hazard ratio (95% CI)	Median survival from BCBM diagnosis (months) (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Time of BCBM diagnosis						
BCBM1 cohort (BCBM at ABC diagnosis)	85		26.2 (19.5–34.7)	<0.0001		
BCBM2 cohort (BCBM after ABC diagnosis)	261	2.261 (1.701, 3.005)	9.0 (6.7–11.8)		2.625 (1.914, 3.599)	<0.001
Number of BCBM lesions						
Only 1	118		22.0 (14.5–27.4)	0.0007		
2 or more	197	1.557 (1.205, 2.013)	8.7 (6.1–13.7)		1.614 (1.230, 2.118)	0.0006
Age at BCBM diagnosis	345	1.006 (0.997, 1.016)		0.1832	1.015 (1.005, 1.026)	0.0041
HER2						
Positive	108		23.4 (18.5–28.0)	<0.0001		
Negative	219	1.880 (1.442, 2.453)	8.0 (6.0–12.2)		2.342 (1.763, 3.111)	<0.001
HR						
Positive	240		12.2 (8.7–16.9)	1		
Negative	105	1.000 (0.778, 1.285)	14.2 (9.0–21.3)		1.230 (0.940, 1.609)	0.1314

[a]Saturated model.
ABC, advanced breast cancer; BCBM, breast cancer brain metastases; BCBM1, brain metastases at advanced breast cancer diagnosis; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

reported LMD (11% of CNS recurrences), further granularity is needed to fully understand this type of involvement.[26] In fact, in our clinical practice, confirmation by positive CSF cytology is scarce, and neuroimaging findings represent an elective method.

Regarding the first breast cancer recurrence in the CNS, the BCBM1 cohort revealed that 26% of the patients experienced isolated BCBM, while 51% had concurrent visceral metastases. Interestingly, 30% of these patients had the TN subtype and 12% had the HR−/HER2+ subtype. Examining outcomes with the current standard of care for patients with HER2+ and TN subtypes treated in the neoadjuvant setting, the KATHERINE trial[27] indicated that 5%–7% of patients with residual disease treated with trastuzumab and T-DM1 in the post-neoadjuvant setting experienced CNS recurrence. Similarly, in the KEYNOTE-522 trial, 2% of patients with TN treated with pembrolizumab experienced CNS recurrence, regardless of the pathological response.[28] These rates, although lower than those in real-world settings, underscore the persistence of CNS recurrence despite modern therapies.[29,30]

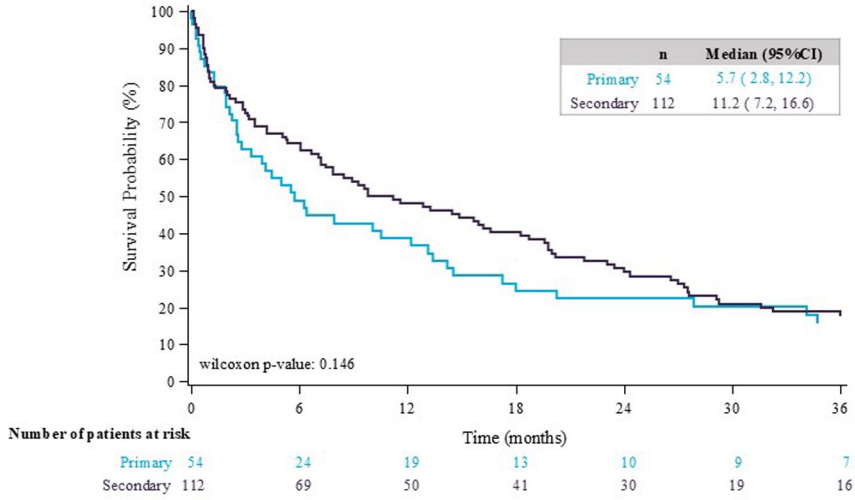


Figure 5. Survival from BCBM diagnosis in patients with the HR+/HER2– subtype by endocrine resistance patterns.
BCBM, breast cancer with brain metastases; HER2, human epidermal growth factor receptor; HR, hormone receptor.

Recent CNS-active therapy trials, such as those of trastuzumab deruxtecan in the DESTINY-Breast program[30–32] and tucatinib in the HER2CLIMB CNS subset,[33] have demonstrated clinically meaningful activity in patients with BCBM, reflecting the rapid evolution of therapeutic options in this setting. As RegistEM is a prospective and ongoing registry, it offers the possibility of capturing how the integration of these novel agents modifies treatment patterns, disease courses, and outcomes in patients with ABC and CNS involvement in future analyses.

In this analysis of the RegistEM study, we provide preliminary real-world data on patterns of endocrine resistance in patients with HR+/HER2− BCBM, using the ABC5 clinical classification.[12] A high prevalence of endocrine resistance was observed, with primary resistance associated with a shorter time to CNS involvement and a trend toward poorer survival. Although not statistically significant, this trend may have important clinical implications and warrants further investigation. These findings could support the relevance of endocrine resistance profiling to guide treatment sequencing and CNS surveillance in the evolving landscape of endocrine- and targeted therapy-based strategies increasingly used prior to chemotherapy or ADCs in HR+/HER2− breast cancer.

The perspective of cumulative BCBM incidence in the RegistEM study aligns with findings from larger cohorts,[17,20] reassuring that the dynamic evolution of breast cancer recurrence throughout the disease depends on the biological subtype.

Survival after BCBM diagnosis in the RegistEM dataset differs from that in some previously reported series.[17,18] These differences likely reflect the introduction of novel therapies, especially for HR+/HER2− and HR−/HER2+ subtypes, into clinical practice since 2016. It is important to note that our study did not specifically evaluate CNS metastases, and certain variables with potential prognostic impact, such as PS or BCBM-related symptoms, could not be assessed. When comparing survival outcomes between the BCBM1 and BCBM2 cohorts with those of patients without CNS involvement by breast cancer subtype, the results for patients with TN highlight the challenges posed by this hard-to-treat disease.

We offer a contemporary perspective from an ABC registry, focusing on patients with BCBM. Expanding on prior research, we analyzed metastatic scenarios since 2016. The RegistEM study, a national multicenter database in Spain, reflects the dynamic healthcare landscape, ensuring patients' follow-up post-ABC diagnosis for ongoing updates and a comprehensive understanding of the evolving ABC landscape. While our results provide practice-oriented information relevant from a clinical perspective, they should be interpreted with caution, given the inherent limitations of observational data and the specificity of the cohort. Some limitations and potential biases

must be acknowledged when putting our findings into context. Our study lacks information on the reasons for BCBM diagnosis, whether due to clinical manifestations or screening procedures; therefore, the potential lead time bias between the BCBM1 and BCBM2 cohorts could not be addressed. We also did not collect data on patients' PS, detailed BCBM anatomical location, or specific local treatments; given the observational nature of the RegistEM study, adverse events could not be recorded. Specifically, we noted that late diagnosis of BCBM in the BCBM2 cohort could lead to an underestimation of survival compared with that of the BCBM1 cohort. Second, a multivariate Cox regression model was used to identify the prognostic factors for survival after BCBM diagnosis. The evaluation of the CNS response was not protocolized for each systemic PD and relied on the standard of care within clinical practice management. Third, the RegistEM population may also underrepresent patients with rapidly deteriorating conditions, particularly those with poor PS. Despite the inclusion criteria requiring all patients to be diagnosed with ABC within a given year, and regular reminders to study investigators to include deceased patients, the possibility of residual bias cannot be entirely ruled out. Another important limitation was the lack of ethnic and geographic diversity, as the cohort was predominantly Caucasian, which did not allow us to generalize our findings. Finally, the exploratory analysis of primary versus secondary endocrine resistance, aimed at capturing insights into the underlying biology of HR+/HER2− breast cancer, was underpowered and not statistically prespecified. Therefore, these findings should be interpreted with caution and considered hypothesis-generating rather than conclusive.

Nevertheless, the comprehensive clinical information and long-term follow-up provided by RegistEM offer meaningful insights into the real-world patterns and outcomes of BCBM. Continued efforts through observational registries and prospective clinical trials are essential to improve CNS management strategies adapted to each breast cancer subtype.

Conclusion

CNS metastases represent a significant healthcare burden for patients with ABC, with a CuIn that increases over time in a subtype-dependent manner. Patients with TN or HER2+ disease develop BCBM earlier and have poorer outcomes than those with other breast cancer subtypes. In our cohort, patients with BCBM at the time of ABC diagnosis had markedly longer survival than those who developed it later. An exploratory analysis of patients with HR+ breast cancer revealed that endocrine resistance, particularly primary resistance, was frequently associated with earlier BCBM and shorter survival. Further investigations are warranted to explore novel strategies for preventing BCBM and improving outcomes in this population.

Authors' note

The first results of this analysis were reported at the San Antonio Breast Cancer Symposium in 2021 in a poster spotlight session on brain metastases (Cancer Res (2022) 82 (4_Supplement): PD4-08; https://doi.org/10.1158/1538-7445.SABCS21-PD4-08).

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the IRB of the Hospital Universitario Fundación Alcorcón (Madrid, Spain) according to the applicable legislation. Written informed consent was obtained from all patients, although some exceptions were authorized by the IRB for patients who died.

Consent for publication

None.

Author contributions

Sara López-Tarruella: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Ángel Guerrero-Zotano: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft.

Silvia Antolín: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Josefina Cruz: Investigation; Resources; Writing – review & editing.

Purificación Martínez: Investigation; Resources; Writing – review & editing.

César A. Rodríguez: Investigation; Resources; Writing – review & editing.

Catalina Falo: Investigation; Resources; Writing – review & editing.

Álvaro Rodríguez-Lescure: Investigation; Resources; Writing – review & editing.

Encarna Adrover: Investigation; Resources; Writing – review & editing.

María Hernández: Investigation; Resources; Writing – review & editing.

Raquel Andrés: Investigation; Resources; Writing – review & editing.

J. Ignacio Chacón: Investigation; Resources; Writing – review & editing.

José Luis Alonso Romero: Investigation; Resources; Writing – review & editing.

Ana Miguel: Methodology; Resources; Writing – review & editing.

César Gómez-Raposo: Investigation; Resources; Writing – review & editing.

Mireia Margelí: Investigation; Resources; Writing – review & editing.

Iria González: Investigation; Resources; Writing – review & editing.

Juan Antonio Guerra: Investigation; Resources; Writing – review & editing.

Antonio Antón: Investigation; Resources; Writing – review & editing.

Ariadna Tibau: Conceptualization; Investigation; Methodology; Resources; Supervision; Writing – review & editing.

Juan José Miralles: Data curation; Formal analysis; Writing – review & editing.

María José Escudero: Data curation; Formal analysis; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

Susana Bezares: Funding acquisition; Project administration; Visualization; Writing – original draft; Writing – review & editing.

Federico Rojo: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Visualization; Writing – review & editing.

Isabel Álvarez: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Acknowledgements

We acknowledge all the patients, investigators, their teams, and all GEICAM staff involved for their collaboration. SAGE Author Services has reviewed the English style.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: RegistEM was funded by Roche Farma, S.A.; Novartis Farmacéutica, S.A.; Celgene, S.L. (a BMS company); Pfizer, S.L.U.; AstraZeneca Farmacéutica Spain, S.A. in alliance with Daiichi Sankyo Spain, S.A.U.; Lilly, S.A.U.; Seagen, S.L.U.; Gilead Sciences, S.L.; and Stemline Therapeutics Switzerland GmbH, an affiliate of the A. Menarini Industrie Farmaceutiche Riunite S.r.L.

Competing interests

S.L.-T. participated in the advisory boards of AstraZeneca, Daiichi Sankyo, Gebro Pharma, Gilead, GSK, Lilly, Menarini_Stemline, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, and Veracyte. She received speaker honoraria from Lilly. She is a member of the board of directors of the Spanish Society of Medical Oncology (SEOM) and GEICAM and the Spanish Breast Cancer Group. S.A. participated in the advisory boards of Roche, Daiichi Sankyo, Pierre Fabre, and Lilly. She participated in speakers' bureaus at Roche, Pierre Fabre, Novartis, and Pfizer. J.C. participated in the advisory boards of AstraZeneca, Roche, Novartis, PharmaMar, Eisai, Lilly, Glaxo, Pfizer, Gilead, Deciphera, Seagen, and Daichii Sankyo. She received speaker honoraria from AstraZeneca, Roche, Novartis, PharmaMar, Eisai, Lilly, Daiichi Sankyo, Seagen, Gilead, and Pfizer. P.M. participated in the advisory boards of Pfizer. She received speaker honoraria from Pfizer, Novartis, Lilly, Roche, MSD, Daiichi Sankyo, AstraZeneca, Rovi, and Leo Pharma. Grant support was received from Pfizer, Novartis, Lilly, Roche, MSD, Daiichi Sankyo, AstraZeneca,

and Leo Pharma. C.A.R. has participated in the advisory boards of Novartis, Lilly, Daiichi Sankyo, MSD, Pierre Fabre, Gilead, and AstraZeneca. He received speaker honoraria from Novartis, Pfizer, Lilly, AstraZeneca, Daiichi Sankyo, MSD, Veracyte, Roche, Eisai, Gilead, and Seagen. C.F. received travel support from Gilead, Pfizer, and Novartis to attend medical conferences. E.A. received speaker honoraria from Lilly and AstraZeneca. She received travel support from Daiichi Sankyo to attend medical conferences. M.H. received honoraria from Pfizer, Roche, AstraZeneca, Daiichi Sankyo, Gilead, and Lilly. She participated in Seagen's advisory board. She received travel support from Pfizer, Roche, AstraZeneca-Daiichi Sankyo, and Lilly to attend medical conferences. C.G.-R. participated in GSK's advisory board. He has received speaker honoraria from AstraZeneca and PharmaMar. He received travel support from GSK to attend medical conferences. M.M. participated in the advisory boards of Novartis, Lilly, Pierre Fabre, Daiichi Sankyo, and Menarini. She received speaker honoraria from Pfizer, Novartis, and Lilly. She received travel support from Gilead, Pfizer, and Roche to attend medical conferences. Her institution received grants from Pfizer, Lilly, Novartis, Eisai, Daiichi Sankyo, AstraZeneca, Gilead, Roche, and Seagen. I.G. received honoraria from Pfizer. A.A. received honoraria from Lilly, Pfizer, Seagen, Novartis, Roche, Gilead, and Daiichi Sankyo. He participated in the advisory boards of AstraZeneca, Daiichi Sankyo, Eli Lilly, and Gilead. He received speaker honoraria or expert testimony from AstraZeneca, Daiichi Sankyo, Eli Lilly, Pfizer, Seagen, Roche, and Novartis. A.T. received honoraria from Lilly and Novartis. She participated in Seagen's advisory board. She received travel support from Novartis, Daiichi Sankyo, and AstraZeneca to attend medical conferences. F.R. participated in the advisory boards of Roche, BMS, MSD, AstraZeneca, Menarini, Novartis, Pfizer, AbbVie, Merck, Amgen, Janssen, Lilly, Sophia Genetics, Daiichi Sankyo, GSK, Pierre Fabre, and Astellas. He received travel support from Menarini, AstraZeneca, and MSD to attend medical conferences. Grant support was received from AstraZeneca, Menarini, Pfizer, Roche, and Novartis. S.B., J.J.M., and M.J.E. are employees of GEICAM. The remaining authors declare no conflicts of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID iDs

Sara López-Tarruella https://orcid.org/0000-0002-2606-9538

Josefina Cruz https://orcid.org/0000-0001-6398-1641

Álvaro Rodríguez-Lescure https://orcid.org/0000-0002-6823-5290

Ariadna Tibau https://orcid.org/0000-0003-0229-6987

Supplemental material

Supplemental material for this article is available online.

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan Detroit cancer surveillance system. *J Clin Oncol* 2004; 22: 2865–2872.
2. Gauthier H, Guilhaume MN, Bidard FC, et al. Survival of breast cancer patients with meningeal carcinomatosis. *Ann Oncol* 2010; 21: 2183–2187.
3. Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. *Neuro-Oncology* 2021; 23: 894–904.
4. Martin AM, Cagney DN, Catalano PJ, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. *JAMA Oncol* 2017; 3: 1069–1077.
5. Wang XY, Rosen MN, Chehade R, et al. Analysis of rates of brain metastases and association with breast cancer subtypes in Ontario, Canada. *JAMA Netw Open* 2022; 5: e2225424.
6. Pestalozzi BC, Zahrieh D, Price KN, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol* 2006; 17: 935–944.
7. Slimane K, Andre F, Delaloge S, et al. Risk factors for brain relapse in patients with

metastatic breast cancer. *Ann Oncol* 2004; 15: 1640–1644.

8. Caswell-Jin JL, Sun LP, Munoz D, et al. Analysis of breast cancer mortality in the US—1975 to 2019. *JAMA* 2024; 331: 233.
9. Sperduto PW, Mesko S, Li J, et al. Beyond an updated graded prognostic assessment (breast GPA): a prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. *Int J Radiat Oncol Biol Phys* 2020; 107: 334–343.
10. Corti C, Antonarelli G, Criscitiello C, et al. Targeting brain metastases in breast cancer. *Cancer Treat Rev* 2022; 103: 102324.
11. Müller V, Bartsch R, Lin NU, et al. Epidemiology, clinical outcomes, and unmet needs of patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases: a systematic literature review. *Cancer Treat Rev* 2023; 115: 102527.
12. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; 31: 1623–1649.
13. Von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; 335: 806–808.
14. Raghavendra AS and Ibrahim NK. Breast cancer brain metastasis: a comprehensive review. *JCO Oncol Pract* 2024; 20: 1348–1359.
15. He Y, Shao Y, Chen Q, et al. Brain metastasis in de novo stage IV breast cancer. *Breast* 2023; 71: 54–59.
16. Sun M-S, Yun Y-Y, Liu H-J, et al. Brain metastasis in de novo breast cancer: an updated population-level study from SEER database. *Asian J Surg* 2022; 45: 2259–2267.
17. Darlix A, Louvel G, Fraisse J, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. *Br J Cancer* 2019; 121: 991–1000.
18. Witzel I, Laakmann E, Weide R, et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. *Eur J Cancer* 2018; 102: 1–9.
19. Hurvitz SA, O'Shaughnessy J, Mason G, et al. Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. *Clin Cancer Res* 2019; 25: 2433–2441.
20. Sammons SL, Sanglier T, Leone JP, et al. Prevalence by therapy line and incidence of breast cancer brain metastases in 18 075 patients. *J Natl Cancer Inst* 2025; 117: 1565–1572.
21. Epaillard N, Lusque A, Jacot W, et al. Incidence and outcome of brain and/or leptomeningeal metastases in HER2-low metastatic breast cancer in the French ESME cohort. *ESMO Open* 2024; 9: 103447.
22. Pasquier D, Darlix A, Louvel G, et al. Treatment and outcomes in patients with central nervous system metastases from breast cancer in the real-life ESME MBC cohort. *Eur J Cancer* 2020; 125: 22–30.
23. Garcia-Saenz JA, Blancas I, Echavarria I, et al. SEOM–GEICAM–SOLTI clinical guidelines in advanced breast cancer (2022). *Clin Transl Oncol* 2023; 25: 2665–2678.
24. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30: 1194–1220.
25. Barcenas CH, Song J, Murthy RK, et al. Prognostic model for de novo and recurrent metastatic breast cancer. *JCO Clin Cancer Inform* 2021; 5: 789–804.
26. Fitzpatrick A, Iravani M, Mills A, et al. Genomic profiling and pre-clinical modelling of breast cancer leptomeningeal metastasis reveals acquisition of a lobular-like phenotype. *Nat Commun* 2023; 14: 7408.
27. Geyer CE, Untch M, Huang C-S, et al. Survival with trastuzumab emtansine in residual HER2-positive breast cancer. *N Engl J Med* 2025; 392: 249–257.
28. Pusztai L, Denkert C, O'Shaughnessy J, et al. Event-free survival by residual cancer burden with pembrolizumab in early-stage TNBC: exploratory analysis from KEYNOTE-522. *Ann Oncol* 2024; 35: 429–436.
29. Pérez-García JM, Vaz Batista M, Cortez P, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: the DEBBRAH trial. *Neuro-Oncology* 2023; 25: 157–166.
30. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med* 2024; 30: 3717–3727.

31. Bartsch R, Pérez-García JM, Furtner J, et al. Results of a patient-level pooled analysis of three studies of trastuzumab deruxtecan in HER2-positive breast cancer with active brain metastasis. *ESMO Open* 2025; 10: 104092.

32. André F, Cortés J, Curigliano G, et al. A pooled analysis of trastuzumab deruxtecan in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer with brain metastases. *Ann Oncol* 2024; 35: 1169–1180.

33. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB randomized clinical trial. *JAMA Oncol* 2023; 9: 197–205.