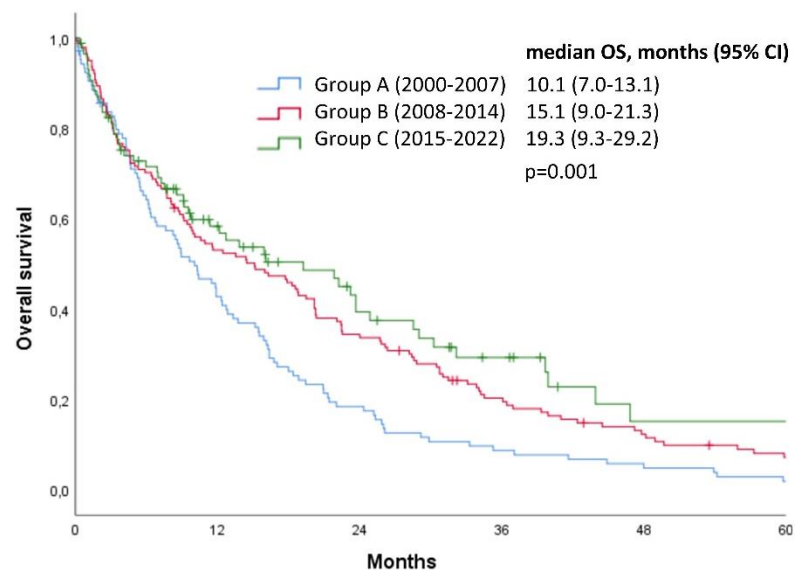


Supplementary Table 1. Patient distribution in the three time intervals according to the participating center.

Subtype	Group A (2000-2007) N=241	Group B (2008-2014) N=323	Group C (2015-2022) N=215	Total
Istituto Oncologico Veneto	50	123	202	375
Montpellier Cancer Institute	108	179	13	300
Center Antoine Lacassagne	83	21	0	104

Supplementary Figure 1. Overall survival according to year of diagnosis of brain metastases in patients with HER2+ breast cancer (both HR+ and HR-).



Supplementary Table 2. Cause of death in the three time intervals according to BC subtype.

Subtype	Cause of death	Group A (2000-2007) N=230 (%)	Group B (2008-2014) N=308 (%)	Group C (2015-2022) N=165 (%)	p value
HR+/HER2-	Brain progression	33 (47.1)	40 (39.2)	21 (29.2)	0.492
	Other	30 (42.9)	44 (43.1)	30 (41.6)	
	Missing	7 (10.0)	18 (17.6)	21 (29.2)	
HR+/HER2+	Brain progression	20 (51.3)	21 (31.3)	14 (40.0)	0.715
	Other	13 (33.3)	20 (29.9)	12 (34.3)	
	Missing	6 (15.4)	26 (38.8)	9 (25.7)	
HR-/HER2+	Brain progression	34 (53.1)	27 (42.2)	9 (47.4)	0.984
	Other	24 (37.5)	19 (29.7)	7 (36.8)	
	Missing	6 (9.4)	18 (28.1)	3 (15.8)	
HR-/HER2-	Brain progression	34 (59.6)	34 (45.3)	22 (56.4)	0.846
	Other	22 (38.6)	24 (32.0)	12 (30.8)	
	Missing	1 (1.8)	17 (22.7)	5 (12.8)	

Abbreviations: HR Hormone Receptors

Supplementary Table 3. Univariate and multivariate Cox proportional hazards model for OS in group A

	Median OS, months (95% CI)	Univariate Cox hazard ratio (95% CI)	p value	Multivariate Cox hazard ratio (95% CI)	p value
Age					
≤50	12.8 (9.4-16.3)	0.59 (0.45-0.77)	<0.001	0.60 (0.45-0.79)	0.005
>50	5.7 (4.6-6.9)	Ref.		Ref.	
HR					
Positive	9.1 (6.2-12.0)	0.87 (0.67-1.13)	0.290		
Negative	6.9 (4.5-9.3)	Ref.			
HER2					
Positive	10.1 (7.0-13.1)	0.99 (0.76-1.29)	0.958		
Negative	6.5 (4.4-8.6)	Ref.			
KPS					
90-100	15.6 (10.9-20.3)	0.22 (0.15-0.32)	<0.001	0.24 (0.16-0.36)	<0.001
70-80	11.5 (9.2-13.8)	0.32 (0.23-0.44)		0.33 (0.24-0.46)	
≤60	2.5 (1.2-3.9)	Ref.		Ref.	
Stage at BC diagnosis					
IV	8.2 (5.5-10.9)	0.88 (0.74-1.05)	0.161		
non-IV	8.4 (6.0-10.8)	Ref.			
BMs at first diagnosis of mBC					
Yes	10.8 (6.1-15.5)	0.65 (0.49-0.87)	0.003	0.81 (0.56-1.17)	0.263
No	6.5 (4.7-8.3)	Ref.		Ref.	
Number of BMs					
1	15.1 (9.0-21.1)	0.63 (0.45-0.88)	0.040	0.37 (0.59-1.22)	0.696
2	9.6 (5.7-13.5)	0.79 (0.55-1.13)		0.83 (0.58-1.20)	
3	11.9 (5.1-18.7)	0.72 (0.45-1.17)		0.94 (0.56-1.57)	
>3	6.2 (4.3-8.2)	Ref.		Ref.	
Extracranial metastases					
Absent	21.6 (10.1-33.1)	0.50 (0.33-0.77)	0.001	0.80 (0.48-1.33)	0.383
Present	6.7 (5.0-8.5)	Ref.		Ref.	

Abbreviations: OS Overall Survival, CI Confidence Interval, HR Hormone Receptor, KPS Karnofsky Performance Status, BMs Brain Metastases

Supplementary Table 4. Univariate and multivariate Cox proportional hazards model for OS in group B

	Median OS, months (95% CI)	Univariate Cox hazard ratio (95% CI)	p value	Multivariate Cox hazard ratio (95% CI)	p value
Age					
≤50	10.9 (8.4-13.5)	0.77 (0.60-0.97)	0.030	0.88 (0.68-1.14)	0.346
>50	6.9 (4.8-9.1)	Ref.		Ref.	
HR					
Positive	9.8 (8.2-11.4)	0.95 (0.76-1.19)	0.642		
Negative	7.4 (5.3-9.5)	Ref.			
HER2					
Positive	15.1 (9.0-21.3)	0.54 (0.43-0.68)	<0.001	0.54 (0.42-0.69)	<0.001
Negative	5.8 (3.9-7.7)	Ref.		Ref.	
KPS					
90-100	18.3 (12.3-24.3)	0.27 (0.19-0.38)	<0.001	0.27 (0.19-0.39)	<0.001
70-80	10.6 (8.4-12.9)	0.35 (0.27-0.46)		0.33 (0.25-0.45)	
≤60	3.0 (2.1-3.8)	Ref.		Ref.	
Stage at BC diagnosis					
IV	12.1 (4.8-19.3)	0.88 (0.77-1.02)	0.090	0.84 (0.62-1.13)	0.247
non-IV	8.0 (6.3-9.8)	Ref.		Ref.	
BMs at first diagnosis of mBC					
Yes	12.7 (3.4-22.0)	0.63 (0.48-0.82)	0.001	0.62 (0.44-0.87)	0.005
No	7.7 (5.8-9.6)	Ref.		Ref.	
Number of BMs					
1	11.4 (4.2-18.5)	0.62 (0.48-0.81)		0.70 (0.53-0.94)	
2	6.4 (2.5-10.3)	0.95 (0.68-1.34)	0.006	0.81 (0.56-1.16)	0.115
3	8.7 (4.4-12.9)	0.86 (0.54-1.36)		0.90 (0.56-1.45)	
>3	7.5 (5.5-9.5)	Ref.		Ref.	
Extracranial metastases					
Absent	12.7 (0.0-27.3)	0.60 (0.41-0.87)	0.007	1.03 (0.63-1.69)	0.906
Present	8.2 (6.4 -10.0)	Ref.		Ref.	

Abbreviations: OS Overall Survival, CI Confidence Interval, HR Hormone Receptor, KPS Karnofsky Performance Status, BMs Brain Metastases

Supplementary Table 5. Univariate and multivariate Cox proportional hazards model for OS in group C

	Median OS, months (95% CI)	Univariate Cox hazard ratio (95% CI)	p value	Multivariate Cox hazard ratio (95% CI)	p value
Age					
≤50	12.7 (5.2-20.2)	0.66 (0.48-0.92)	0.012	0.74 (0.52-1.07)	0.109
>50	6.1 (3.2-9.1)	Ref.		Ref.	
HR					
Positive	8.6 (5.8-11.5)	1.06 (0.77-1.50)	0.721		
Negative	7.9 (2.7-13.2)	Ref.			
HER2					
Positive	19.3 (9.3-29.2)	0.52 (0.38-0.72)	<0.001	0.50 (0.34-0.73)	<0.001
Negative	5.0 (3.4-6.7)	Ref.		Ref.	
KPS					
90-100	25.2 (18.7-31.7)	0.14 (0.09-0.22)	<0.001	0.14 (0.08-0.23)	<0.001
70-80	7.3 (4.2-10.4)	0.32 (0.21-0.47)		0.32 (0.21-0.48)	
≤60	2.0 (1.2-2.8)	Ref.		Ref.	
Stage at BC diagnosis					
IV	10.4 (5.1-15.8)	0.88 (0.74-1.05)	0.146		
non-IV	6.7 (3.4-10.0)	Ref.			
BMs at first diagnosis of mBC					
Yes	16.1 (2.1-30.1)	0.62 (0.43-0.88)	0.008	0.77 (0.50-1.18)	0.231
No	7.0 (4.0-9.9)	Ref.		Ref.	
Number of BMs					
1	15.9 (6.7-25.2)	0.50 (0.35-0.71)		0.59 (0.39-0.89)	
2	10.6 (4.3-16.9)	0.79 (0.49-1.27)	<0.001	0.60 (0.36-1.02)	0.007
3	3.7 (1.1-6.2)	1.51 (0.84-2.72)		1.57 (0.81-2.81)	
>3	4.2 (2.5-5.8)	Ref.		Ref.	
Extracranial metastases					
Absent	27.6 (20.4-34.8)	0.41 (0.24-0.68)	<0.001	0.84 (0.45-1.57)	0.583
Present	7.0 (4.5 -9.4)	Ref.		Ref.	

Abbreviations: OS Overall Survival, CI Confidence Interval, HR Hormone Receptor, KPS Karnofsky Performance Status, BMs Brain Metastases

Supplementary Figure 2. Overall survival according to Updated breast GPA score in different time intervals. Kaplan-Meier curves showing overall survival from time of brain metastases diagnosis according to Updated breast GPA score in the overall population (A), in cohort A (B), in cohort B (C) and in cohort C (D).

