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Continued Endocrine Therapy Is Associated with Improved Survival in Patients with Breast Cancer Brain Metastases

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Abstract

Purpose: Brain metastases (BMs) are a rare but devastating condition in estrogen receptor (ER)–positive metastatic breast cancer (MBC). Although endocrine therapy (ET) is the mainstay of treatment in this disease subtype, only case reports have been published concerning the activity of ET in BMs henceforth. Therefore, we aimed to systematically investigate the impact of ET after diagnosis of BM on outcome and clinical course of disease in patients with ER-positive MBC.

Experimental Design: Patient characteristics, detailed information about BMs including diagnosis-specific graded prognostic assessment class (DS-GPA), and clinical outcome were obtained by retrospective chart review for all patients treated for ER-positive breast cancer BMs between 1990 and 2017 at an academic care center. Overall survival (OS) was measured as the interval from diagnosis of BM until death or last date of follow-up.

Results: Overall, 198 patients [female: 195/198 (98.5%); male: 3/198 (1.5%)] with ER-positive breast cancer BMs were available for this analysis. Eighty-eight of 198 patients (44.4%) received ET after diagnosis of BM including aromatase inhibitors (AIs; letrozole, anastrozole, exemestane), tamoxifen, and fulvestrant. Median OS was significantly longer in patients receiving ET after diagnosis of BM compared with patients who did not (15 vs. 4 months, $P < 0.001$; log-rank test). No significant difference in terms of OS was observed between patients receiving AIs, tamoxifen, or fulvestrant. In patients with concomitant leptomeningeal carcinomatosis (LC), ET prolonged median OS significantly as well (7 vs. 3 months, $P = 0.012$; log-rank test). In a multivariate analysis including DS-GPA and ET, only treatment with ET after diagnosis of BM (HR, 0.69; 95% confidence interval, 0.48–0.99; $P = 0.046$) was associated with prognosis (Cox regression model).

Conclusions: Continuing ET after BM diagnosis was associated with a significantly prolonged OS in this large single-center cohort. No substantial differences between substances were observed. These findings should be validated in a prospective cohort.

Introduction

Up to 15% of patients with metastatic breast cancer (MBC) will develop brain metastases (BMs) during their course of disease, making MBC the second most common cause of BMs among all solid malignancies (1). Over the last decades, prognosis of MBC has remarkably improved due to advances in systemic treatment (2, 3). Nevertheless, prognosis of patients with BM remains dismal with median overall survival (OS) times ranging from 2 to 16 months (1). Patients with triple-negative tumors are at higher risk of being diagnosed with BM compared with luminal or HER2-positive disease (4). Patients with HER2-positive breast cancer, on the other hand, have a higher incidence of BM than patients with HER2-negative disease (5). In addition, BM-free survival was shown to be significantly shorter in triple-negative as well as HER2-positive disease with 14 and 18 months, respectively, compared with 34 months in luminal MBC (6).

Local treatments for MBC BM include whole-brain radiation therapy (WBRT), surgical resection, and stereotactic radiosurgery depending on clinical presentation and BM number. Despite high local remission rates, these interventions extend OS by a few months only. Due to a disruption of the blood–brain/tumor barrier at metastatic sites, even large molecules may penetrate into the central nervous system (CNS) rendering systemic therapies a potential treatment option (7, 8). Although chemotherapy was shown to have only limited OS impact, the application of targeted therapies including HER2-directed drugs was recently reported to result in reasonable intracranial response rates and prolongation of OS (9–11). In estrogen receptor (ER)–positive/HER2-negative disease, BMs are frequently a late event and commonly resemble an advanced disease stage resistant against the majority of endocrine therapy (ET) options. Recently, inhibitors of the mTOR and cyclin-dependent kinase 4 and 6 (CDK4/6)

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Translational Relevance

The present retrospective analysis investigated the association of administering endocrine therapy after diagnosis of brain metastases with overall survival in patients with luminal metastatic breast cancer, and our data suggest that this treatment approach may offer relevant clinical activity and may improve outcome. Of note, this is the first study addressing this topic; still, validation of our results in the context of prospective trials is warranted as this analysis is limited by its retrospective, single-center design. Activity of endocrine therapy in breast cancer brain metastases may have impact on daily treatment practice as clinical data regarding the optimal systemic treatment strategies in breast cancer brain metastases beyond HER2-positive disease is scarce. In this context, elucidating the potential mechanism of action of endocrine therapy in brain metastases and its ability to cross the blood–brain barrier is required to guide future trial planning. In addition, the combination of antihormonal treatment with inhibitors of mTOR and CDK4/6 needs to be mentioned as such endocrine combinations may overcome resistance to endocrine therapy also in brain metastases and may therefore help in establishing endocrine treatment in this patient subset.

were shown to overcome endocrine resistance leading to surging interest regarding the effect of ET on BM.

To our best knowledge, so far only case reports exist focusing on the effect of ET in patients with ER-positive MBC BM. Therefore, we aimed to investigate the impact of ET on OS after diagnosis of BM in a large single-center cohort.

Materials and Methods

Patients

Overall, 277 patients treated between 1990 and 2017 for ER-positive breast cancer BM at the Medical University of Vienna were identified from our database. Seventy-five patients with luminal B/HER2-positive disease were excluded from this analysis due to the dramatically differing survival prognosis of luminal B/HER2-positive to luminal/HER2-negative patients (12). Given the high intracranial efficacy of HER2-targeted therapies, ET is currently a rather uncommon approach in the particular population of patients with luminal MBC BM. Four more patients had to be excluded due to incomplete information regarding hormone receptor status. Therefore, 198 patients were available for this retrospective analysis (Fig. 1). For 28 patients who were diagnosed before 1999, IHC staining for HER2 was not available. None of these patients received HER2-directed therapy. If leptomeningeal carcinomatosis (LC) was present concomitantly to diagnosis of parenchymal BM, patients were also eligible for analysis. If patients underwent MRI evaluation within 8 weeks before death and cerebral progression was evident, we assumed BM as leading cause of death. Information relating to patient demographics, case history, and survival was collected by retrospective chart review. This study was conducted in accordance with the Declaration of Helsinki, and approval by the Institutional Review Board (IRB) was obtained. According to the IRB, no written consent from the subjects was necessary.

All patients were managed by a dedicated team of MBC specialists at an academic breast center; treatment decisions were taken in an interdisciplinary tumor conference. Treatment was performed according to best clinical evidence and according to current standard of care. Brain imaging with MRI was only performed when clinically indicated by neurological symptoms.

Hormone receptor and HER2 status

Receptor status was obtained by chart review as the vast majority had been diagnosed inhouse at the certified Department of Pathology, Medical University of Vienna, according to international guidelines. In brief, ER and progesterone receptor (PR) status was assessed by IHC according to recent recommendations of the American Society of Clinical Oncology (ASCO) and the United States and Canadian Academy of Pathology (USCAP) recommendations (refs. 13, 14; CONFIRM SP1 clone for ER and 1E2 clone for PR, respectively, Ventana); hormone receptor expression was estimated as the percentage of positively stained tumor cells. Results were given as 1+, 2+, and 3+ positive or negative staining, with a cutoff value of <10% positive tumor cells (14). HER2 status was assessed by IHC (HER2 clone 4B5, Ventana) and dual-color FISH (PathVision HER2 DNA probe kit, Vysis Inc.; CISH; INFORN HER2 dual ISH, Ventana). Tumors were classified as HER2-positive if they had a staining intensity of 3+ on the Herceptest; tumors with staining intensity of 2+ were tested by FISH for *HER2* DNA amplification (15).

Statistical analysis

OS was defined as interval from first diagnosis of BM until death or last date of follow-up and estimated with the Kaplan–Meier product limit method. To test for differences between OS curves, the log-rank test was used. To test for differences between 2 parameters, the χ^2 test was used for binary variables. Two-tailed P values <0.05 were considered to indicate statistical significance. The association of ET after the diagnosis of BM with outcome was the main point of interest of the present study. Therefore, we predefined *a priori* the inclusion of ET after diagnosis of BM in combination with the well-established diagnosis-specific graded prognostic assessment score (DS-GPA; ref. 16) which includes breast cancer subtype (luminal A, luminal B/Her2-positive, triple-negative breast cancer, and HER2-positive), age (<60 and >60 years), and Karnofsky performance status (<50, 60, 70–80, and 90–100) into the multivariate model. The DS-GPA was included in order to examine the independence of ET application from established prognostic factors. In order to minimize the problem of multiple testing, we restricted the survival analysis to ET after BM and the DS-GPA as a standard prognostic score.

All statistics were calculated using statistical package for the social sciences (SPSS) 24.0 software (SPSS Inc.).

Results

Patient characteristics

One hundred ninety-eight patients with histologically proven MBC BM were available for this analysis. Median age at breast cancer diagnosis was 50 years (range, 22–91). Three patients (1.5%) were male, and 195 patients (98.5%) female. One hundred twenty-two of 198 patients (61.6%) presented with invasive ductal and 38 of 198 patients (19.2%) with invasive lobular carcinoma. Considering patients with stage IV disease at primary diagnosis (28/198; 14.1%), 89 of 198 patients (44.9%) had

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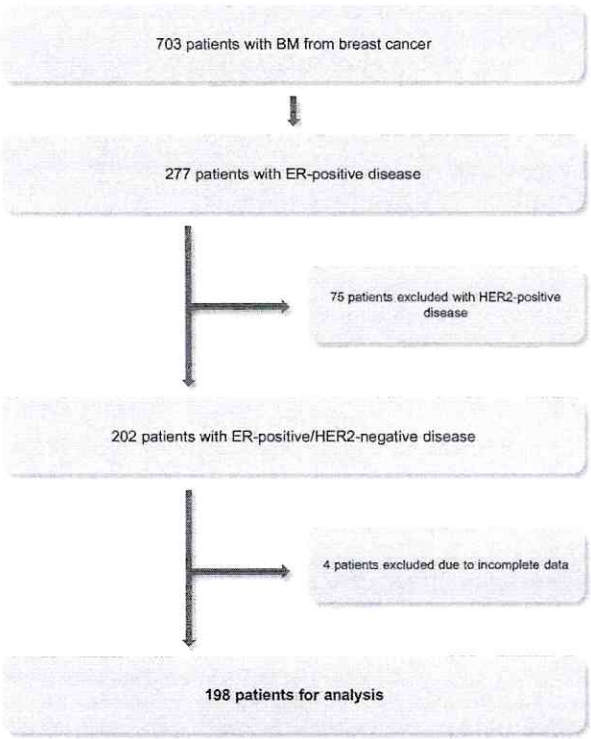

Figure 1.
CONSORT diagram of patients.

received prior adjuvant chemotherapy and 124 of 198 patients (62.6%) adjuvant ET for early breast cancer. Visceral metastases before BM were present in 115 of 198 patients (58.1%). Median time to recurrence from first diagnosis until metastatic disease was 44 months (range 0–352) in the overall patient population. Forty of 198 (20.2%) patients presented with complete remission and no evidence of extracranial disease, 11 of 198 (5.6%) with partial remission, 54 of 198 (27.3%) with stable and 64 of 198 (32.3%) with progressive extracranial disease at diagnosis of BM. Thirty-three of 88 (37.5%) patients receiving ET after BM presented with progressive extracranial disease at diagnosis of BM and 31 of 110 (28.2%) patients not receiving ET after BM diagnosis ($P = 0.112$; χ^2 test). Patient characteristics before development of BM are listed in Table 1 according to ET after diagnosis of BM. Detailed patient characteristics of the overall population are listed in Supplementary Table S1.

Characteristics of BM

Median BM-free survival in the overall population was 14 months (range 0–213). Median DS-GPA class at diagnosis of BM was 2 (range 2–4). Median OS in the overall patient cohort differed statistically significant between DS-GPA classes (11 months for class 2 vs. 3 months for class 3 vs. 12 months for class 4, $P = 0.014$; log-rank test). Concomitant LC at diagnosis of parenchymal BM was present in 30 of 198 patients (15.2%). Within patients with LC at diagnosis of BM, 18 (60.0%) originally had invasive ductal, 11 (36.7%) invasive lobular, and 1 (3.3%) had other specified invasive carcinoma. Progression of BM or local recurrence after initial treatment of BM was observed in 76 of 198 patients (38.4%) and systemic progressive disease after diagnosis of BM in 77 of 198 patients (38.9%). Upfront treatment of BM composed of WBRT in 90 (45.5%), neurosurgical resection in 57 (28.8%), stereotactic radiosurgery in 48 (24.2%), chemotherapy in 1 (0.5%), and best supportive care in 2 (1.0%) of 198 patients. Thirty-eight of 198 patients (19.2%, 147 unknown) are considered to have died due to BM progression, since MRI revealed a cerebral progression within 8 weeks before death.

Effect of ET on the course of disease and OS after BM diagnosis

Eighty-eight of 198 patients (44.4%) received ET after diagnosis of BM. The median number of ET lines applied after diagnosis of BM was 1 (range, 1–4). Eighty-eight patients received at least 1 line ET after diagnosis of BM, 18 of 88 patients (20.5%) 2 lines, and 2 patients (2.3%) 3 lines of ET. Sixty-six of 88 patients (75.0%) received an aromatase inhibitor (including anastrozole, letrozole, exemestane) after diagnosis of BM, 20 patients (22.7%) fulvestrant and 14 patients (15.9%) tamoxifen. Nine (10.2%) premenopausal patients received additionally goserelin as ovarian function suppression. No direct evidence of CNS response to single-agent hormonal therapy was evident in this particular cohort, as all patients received initially local therapy before start of ET.

Median OS among all patients was 8 months (range, 0–144). Median OS was significantly longer in patients receiving ET after diagnosis of BM than in patients without ET (15 vs. 4 months, $P < 0.001$; log-rank test; Fig. 2A). To further investigate the effect of ET, DS-GPA and ET after diagnosis of BM were entered in a multivariate Cox regression model. Here, only treatment with ET after diagnosis of BM remained significant [HR, 0.69; 95% confidence interval (CI), 0.48–0.99; $P = 0.046$, Cox proportional hazards model], whereas DS-GPA class did not present with a statistically significant association with OS prognosis (HR, 1.21; 95% CI, 0.90–1.62; $P = 0.208$; Cox proportional hazards model). Significantly less patients with LC concomitantly diagnosed to solid BM received ET compared with patients with solid BM only (26.7% of patients with concomitant LC vs. 47.6% of patients with solid BM; $P = 0.045$; Fisher exact). Still, also in patients with concomitant LC, median OS was significantly longer if ET was given (7 vs. 3 months, $P = 0.012$, log-rank test; Fig. 2B).

Specific effect of different types of first-line ET on OS after BM diagnosis

Fifty-nine of 88 patients (67.0%) were treated with an aromatase inhibitor, 16 (18.2%) with fulvestrant, and 12 (13.6%) with tamoxifen as first-line ET after diagnosis of BM. Nine patients (10.2%) received goserelin in addition to standard ET due to premenopausal status. Patients characteristics after development of BM treated with ET are listed in Table 2.

In our cohort, the type of first-line ET after diagnosis of BM was not statistically significantly associated with median OS, although a numerical difference was observed between the different ET types as patients treated with tamoxifen presented with the numerically longest OS (median OS, 26 months) followed by patients treated with aromatase inhibitors (median OS, 15 months) and fulvestrant (median OS 7 months; $P = 0.313$; log-rank test; Fig. 2C).

Discussion

Two thirds of all breast cancers belong to the luminal subtype (17, 18). About 2.2% of patients with luminal A tumors and 4.7% with luminal B/HER2-negative tumors will develop BM

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Table 1. Patients' characteristic before BM according to ET after diagnosis of BM

	ET after BM		No ET after BM		
Patient characteristics before BM	***n* = 88**	**% 44.4**	***n* = 110**	**% 55.6**	***P* value**
Gender					
Female	87/88	98.9	108/110	98.2	*0.70*
Male	1/88	1.1	2/110	1.8	
Median age at first diagnosis	50		50		*0.60*
Range	22–91		29–82		
Histology of primary tumor					
Invasive ductal carcinoma	53/88	60.2	69/110	62.7	*0.75*
Invasive lobular carcinoma	19/88	21.6	19/110	17.3	
Others	3/88	3.4	3/110	2.7	
Unknown			*32/198 (16.2%)*		
Grading of primary tumor					
Grade 1	6/88	6.8	3/110	2.7	*0.22*
Grade 2	25/88	28.4	38/110	34.5	
Grade 3	28/88	31.8	27/110	24.5	
Unknown			*71/198 (35.9%)*		
HER2 receptor status					
Negative	76/88	86.4	93/110	84.5	*0.37*
No Her2 status (diagnosis before 2000)	12/88	13.6	14/110	12.7	*0.12*
Unknown			*3/198 (1.5)*		
Distant metastases at diagnosis/stage IV					
Yes	15/88	17.0	13/110	11.8	*0.29*
No	73/88	83.0	97/110	88.2	
Adjuvant chemotherapy					
Yes	38/88	43.2	51/110	46.4	*0.57*
No	30/88	34.1	40/110	36.4	
Unknown + stage IV			*39/198 (19.7%)*		
Adjuvant endocrine therapy					
Yes	54/88	61.2	70/110	63.6	*0.61*
No	13/88	14.8	14/110	12.7	
Unknown + stage IV			*47/198 (23.7%)*		
Adjuvant radiotherapy					
Yes	49/88	55.7	65/110	59.1	*0.83*
No	25/88	28.4	31/110	28.2	
Unknown + stage IV			*34/198 (17.2%)*		
Visceral metastases before BM					
Yes	46/88	52.3	69/110	62.7	*0.23*
No	39/88	44.3	41/110	37.3	
Unknown			*3/198 (1.5%)*		
Systemic disease at diagnosis of BM					
No evidence of extracranial disease and complete remission	*21/88*	*23.9*	*19/110*	*17.3*	*0.043*
Partial remission	*2/88*	*2.3*	*9/110*	*8.2*	
Stable disease	*18/88*	*20.5*	*36/110*	*32.7*	
Progressive disease	*33/88*	*37.5*	*31/110*	*28.2*	
Unknown			*29/198 (14.6%)*		
Progressive extracranial disease at diagnosis of BM					
Yes	*33/88*	*37.5*	*31/110*	*28.2*	*0.112*
No	*41/88*	*46.6*	*64/110*	*58.2*	
Unknown			*29/198 (14.6%)*		
Median metastatic sites	1		2		*0.06*
Range	0–8		0–6		
Median lines of chemotherapy before BM	1		2		*0.008*
Range	0–9		0–9		
Median lines of ET before BM	1		1		*0.97*
Range	0–6		0–6		
Median time to recurrence from first diagnosis until metastases (months)	41		44		*0.84*
Range	0–352		0–352		
Median BM-free survival from metastatic disease until BM (months)	8		16		*0.12*
Range	0–213		0–213		

within 15 years after diagnosis of early breast cancer (19); this is a devastating complication that usually occurs rather late during the course of disease in luminal breast cancer compared with other subtypes (6). Because systemic treatment options improved tremendously over the last years in this MBC subtype and survival rates could be further enhanced, incidence of BM will likely increase in these patients. BMs are a particular challenge in MBC, as approximately half of the patients die from intracranial

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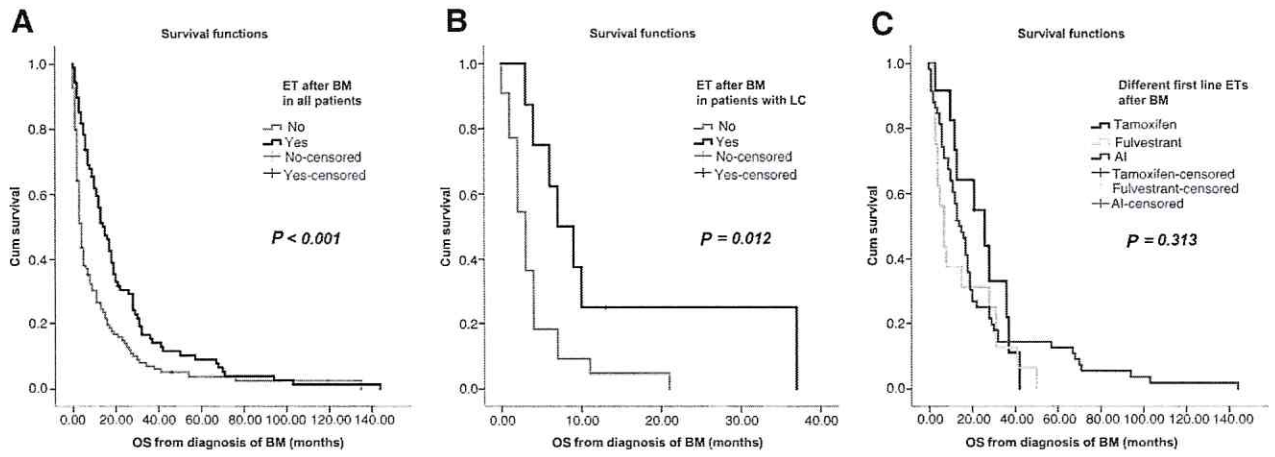

Figure 2.

Kaplan–Meier estimates for OS. **A,** Median OS in overall population according to ET. **B,** Median OS in patients with LC according to ET. **C,** Median OS of patients receiving ET after BM according to different types of first-line ET.

progression while the extracranial disease is stable (20). Local therapy remains the backbone for BM treatment, because only limited data exist on the efficacy of ET in this clinical context (1). Targeted therapies have recently entered the treatment algorithm of breast cancer BM patients as HER2-targeted therapies were shown to generate intracranial responses, prolong OS, and delay WBRT in asymptomatic patients (10, 11). Moreover, the combination of ET with inhibitors of CDK4/6 or mTOR was shown to overcome endocrine resistance leading to growing interest in the systemic treatment of BM and LC in patients with luminal MBC. Therefore, we aimed to investigate the impact of ET on the survival prognosis of MBC BM patients with luminal disease. Of note, this retrospective chart review suggests that patients with further ET after BM diagnosis had a significantly improved outcome.

In this large cohort of patients with ER-positive MBC, ET when given after diagnosis of BM was associated with a significantly prolonged median OS of 15 months. No significant substance-specific differences could be observed between aromatase inhibitors, tamoxifen and fulvestrant. In a multivariate analysis of ET and the well-established prognostic score DS-GPA, only ET after diagnosis remained significant, indicating that ET has an independent survival impact irrespective of the clinical prognostic parameters. So far, prospective studies on the impact of ET in patients with MBC BM are missing, as only some case reports suggest that tamoxifen may offer intracranial activity (21–23). Regarding aromatase inhibitors, 2 case reports showed encouraging OS results when letrozole or anastrozole were administered after diagnosis of BM (24, 25). A third, more recently published case report by Saha and colleagues described a young premenopausal patient with ER-positive metastatic breast cancer who was treated with anastrozole and leuprolide after diagnosis of brain-only relapse in addition to locoregional treatment and still presented with continuous complete remission of her disease 11 years after diagnosis of BM (26).

The blood–brain barrier is frequently discussed as a reason for reduced intracranial efficacy of systemic therapies, and only small studies investigated the brain penetrance of ET. Analysis of brain metastatic tumor and brain tissue specimens of 3 patients revealed an up to 46-fold higher concentration of tamoxifen and its metabolites in BM and healthy brain tissue than in serum

Table 2. Patient characteristics after BM according to ET after diagnosis of BM

	ET after BM		No ET after BM		
Patient characteristics after BM	***n* = 88**	**% 44.4**	***n* = 110**	**% 55.6**	***P* value**
First-line (local) therapies after diagnosis of BM					
Stereotactic radiosurgery	23/88	26.1	25/110	22.7	*0.578*
Chemotherapy	0/88	0.0	1/110	0.9	*0.370*
Surgery	28/88	31.8	29/110	26.4	*0.400*
WBRT	36/88	40.9	54/110	49.1	*0.251*
Best supportive care	1/88	1.1	1/110	0.9	*0.874*
Median lines of ET after diagnosis of BM	1		—		
Range	1–4		—		
First-line ET after diagnosis of BM					
Tamoxifen	12/88	13.6	—		
Anastrozole	29/88	33.0	—		
Exemestane	15/88	17.0	—		
Letrozole	15/88	17.0	—		
Fulvestrant	16/88	18.2	—		
Goserelin for additional OFS	9/88	10.2	—		
Median OS from diagnosis of BM (mo)	15		4		*<0.001*
Range	10–18		3–5		

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samples (27). Moreover, 14C-labeled tamoxifen showed a distribution to the brain in mice, and small amounts of tamoxifen and 4-hydroxy-N-desmethyltamoxifen in human cerebro-spinal fluid could be detected (28, 29). Focusing on the specific mode of action of different types of ET, aromatase inhibitors act by reducing peripheral estrogen production, whereas tamoxifen and fulvestrant directly modify and block ERs. Consequently, aromatase inhibitors might not necessarily need to penetrate the blood–brain/tumor barrier if systemic estrogen production is already being reduced effectively. Nevertheless, there is *in vitro* and *in vivo* data supporting aromatase production and its distribution within the brain (30). Taken together with the observed impact on the survival prognosis, ET could indeed be a viable treatment option that should be investigated in further clinical trials. Furthermore, although BMs develop late in luminal MBC and most patients will have already be pretreated with 1 or more lines of ET, the combination of ET with targeted therapies may be promising.

Even in patients with concomitant LC at diagnosis of BM, ET was associated with a significantly improved median OS in our study. These data support the findings of Boogerd and colleagues (31). In 2 patients, antihormonal therapy yielded a prolonged neurologic response of at least 12 months and an OS of 14 and 19 months, respectively. Based on our findings, ET might be considered for systemic pharmacotherapy, particularly in patients with nodular as well as combined nodular and linear leptomeningeal disease (type B/C LC; ref. 32).

Interestingly, ET showed a significant association with OS despite the fact that most of our patients had received palliative ET before diagnosis of BM in earlier treatment lines, and thus may have developed "secondary" endocrine resistance. Different interactive signaling mechanisms leading to intrinsic and acquired resistance have been described; acquired resistance may be caused by activating estrogen receptor gene (*ESR1*) mutations resulting in constitutive activity of estrogen receptor-α and upregulation of alternative pathways and receptors (33, 34). Furthermore, several signal transducing pathways that cross-talk with ER like PI3K-Akt-mTOR become activated or upregulated during endocrine treatment (35, 36). Phosphorylation of the mTOR complex 1 (mTORC1) for instance might be responsible for ligand-independent activation of ER and can be targeted by mTOR inhibitors such as everolimus (37). Importantly, some preclinical studies indicated that the mTOR pathway might be of therapeutic interest in the particular context of BM (38). Adding CDK 4/6 inhibitors to ETs is a standard treatment approach in HR-positive MBC as the combination was shown to prolong progression-free survival by blocking cell-cycle progression from G_1 to S phase (39–41). Importantly, a recent analysis of matched primary tumor and BM revealed frequently alterations in the CDK pathway, indicating that activation might be involved in the brain metastatic process (42). Interestingly, the CDK4/6 inhibitor abemaciclib was shown to cross the blood–brain barrier in an intracranial glioblastoma xenograft (43). Therefore, combination of ET with targeted therapies such as inhibitors of CDK4/6, mTOR, and PI3K should be considered in future trials of systemic treatment for BM.

Although we were able to investigate the association of ET with survival after diagnosis of BM in a unique and large MBC BM cohort, the results of our analysis have to be interpreted with caution due to the monocentric and the retrospective design of our study. We were able to show that application of ET after diagnosis of BM is independently associated with survival prognosis in a multivariate analysis with the well-established DS-GPA. Although certainly several clinical factors did differ between the ET and non-ET cohort, the DS-GPA includes the most important and repetitive validated clinical prognostic factors in the context of BM. Nevertheless, to our best knowledge this is the so far largest first single-center cohort approaching the topic of ET in the special context of MBC BM, and our data strongly underscore the necessity for prospective clinical trials investigating the therapeutic potential of ET in patients with MBC BM.

In summary, this is the first analysis investigating the effect of ET on OS in patients with MBC after diagnosis of BM. We were able to show a significant association of ET after diagnosis of BM with survival in our uniquely large population of 198 MBC BM patients. Our results underscore that initiation or continuation of (alternative) ET should be considered after diagnosis of BM. However, certainly prospective BM-specific trials or trials with BM-specific endpoints are needed to investigate the therapeutic efficacy of ET in this particular population. Furthermore, insights on the specific molecular mechanisms, potential mechanism of action of ET on BM, and its ability to cross the blood–brain barrier are needed to guide the further clinical trial planning. In addition, studies evaluating the potential combination of ET with CDK4/6 inhibitors and mTOR inhibitors might be of particular interest as these pathways were previously described in the context of BM (42, 44).

Disclosure of Potential Conflicts of Interest

A.S. Berghoff is a consultant/advisory board member for Roche. F. Fitzal reports receiving speakers bureau honoraria from Novartis, Pfizer, AstraZeneca, and Roche, and is a consultant/advisory board member for Pfizer, and Novartis. M. Gnant is an employee of and has ownership interests (including patents) at Sandoz, reports receiving speakers bureau honoraria from Amgen, AstraZeneca, Celgene, Eli Lilly, Novartis, Nanostring Technologies and Roche, and is a consultant/advisory board member for Accelsiors. C.C. Zielinski is a consultant/advisory board member for Roche, Novartis, Bristol-Myers Squibb, Merck Sharp Dohme, Imugene, Ariad, Pfizer, Merrimack, Merck KGaA, Fibrogen, AstraZeneca, Tesaro, and Gilead. G.G. Steger is a consultant/advisory board member for Novartis and Pfizer, and reports receiving commercial research support from AstraZeneca, Novartis, Lilly and Pfizer. M. Preusser is a consultant/advisory board member for Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, and Merck Sharpe & Dome. R. Bartsch is a consultant/advisory board member for Eli Lilly, Novartis, Roche, Pfizer, Daiichi, Celgene, AstraZeneca, and Pierre Febre, and reports receiving commercial research grants from Roche and Novartis. No potential conflicts of interest were disclosed by the other authors.

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