

# Use and Duration of Chemotherapy in Patients With Metastatic Breast Cancer According to Tumor Subtype and Line of Therapy

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## Abstract

Benefits of chemotherapy vary in patients with metastatic breast cancer (MBC). This article describes the impact of tumor subtype and the line of therapy on the duration of chemotherapy. Clinicopathologic characteristics were extracted from the medical records of 199 consecutive patients with MBC at Dana-Farber Cancer Institute and analyzed according to subtype. Tumor subtypes were classified as hormone receptor (HR)–positive, triple-negative (TNBC), or HER2-amplified breast cancer. Duration of chemotherapy of each line was defined as the start of a chemotherapy regimen to the start of the next line of therapy as a result of progression or toxicity. There were 96, 44, and 59 patients with HR<sup>+</sup>, TNBC, and HER2-amplified breast cancer, respectively. Median age at MBC diagnosis was 53 years. Median overall survivals were 32 and 54 months for HER2-amplified disease, 36 months for HR<sup>+</sup> breast cancer, and 17 months for TNBC ( $P < .0001$ ). Patients with HER2-amplified disease received the most lines (median, 4;  $P = .032$ ) and the longest duration of chemotherapy for every line. The median duration of chemotherapy in HER2-amplified patients remained at more than 4 months even out to sixth-line therapy. Patients with TNBC tended to receive the shortest duration of chemotherapy for every line of therapy. Tumor subtypes influence the number of lines, duration of chemotherapy, and survival. Among patients with HR<sup>+</sup> and HER2-amplified disease who undergo chemotherapy beyond the third line, substantial rates of prolonged therapies suggest clinical benefit. The role of advanced (greater than third) chemotherapy lines in improving survival of all patients with MBC warrants further study. (*J Natl Compr Canc Netw* 2014;12:71–80)

## Background

Advances in breast cancer treatment have significantly improved survival for patients with metastatic breast cancer (MBC) from 1 to 2 years in the 1970s to 1 to 3 years today.<sup>1–3</sup> However, MBC remains incurable, and the goals of treatment are prolongation of survival and palliation of symptoms.<sup>4,5</sup>

Although gene profiling studies have advanced the understanding of the heterogeneity of breast cancer,<sup>6,7</sup> most clinicians broadly classify breast cancer into 3 subtypes: hormone receptor (HR)–positive, HER2-amplified, and triple-negative breast cancer (TNBC).<sup>8–11</sup> TNBC is characterized by a younger patient distribution and a higher mortality rate compared with other subtypes.<sup>9,10</sup> HER2 amplification historically conferred a worse prognosis,<sup>12</sup> but this has improved with the introduction of HER2-targeted therapy.<sup>13</sup> HR<sup>+</sup> breast cancers have traditionally been associated with the best prognosis but are characterized by an ongoing risk of late relapse relative to the other subtypes.<sup>14</sup>

Decisions about treatment are increasingly being tailored to individual patient characteristics, such as tumor subtype. This clinical classification identifies targets with established data on treatment efficacy; hormonal therapies for HR<sup>+</sup> breast cancer; and HER2-directed therapies for HER2-amplified breast cancer.<sup>15,16</sup> However, despite the heterogeneity of breast cancer, almost all patients with MBC will receive chemotherapy at some point. Compared with patients who have other solid tumors, patients with MBC have a larger number of therapeutic options available.<sup>17</sup> The likelihood of response and prolonged tumor control is highest with the first line of chemotherapy, with limited data on the efficacy of later lines of chemotherapy despite its very common use in clinical practice.<sup>18–20</sup> Few data also ex-

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ist regarding the impact of tumor subtype on the likelihood of benefit with later lines of treatment. Although some data exist from prospective clinical trials conducted in patients with refractory MBC, there are unavoidable limitations in basing estimates of the benefit of chemotherapy or survival solely on these trials, given that eligibility and exclusion criteria limit the types of patients who enter the trials, and may not be representative of patients with MBC seen in everyday practice.

Patients with advanced cancer want information about their prognosis and what to expect from their disease and treatments.<sup>21,22</sup> A better sense of the likelihood of clinical benefit, survival probabilities, and prognostic factors could inform decisions on whether to embark on another line of palliative chemotherapy.<sup>23</sup> This retrospective study describes the pattern of palliative chemotherapy use according to tumor subtypes in patients treated for MBC between 2004 and 2007, and the duration of chemotherapy as defined by the time from the initiation of one chemotherapy regimen to the initiation of the next line of therapy as a result of disease progression or toxicity.

## Methods

The medical records of 318 consecutive patients diagnosed with MBC between January 1, 2004, and December 31, 2007, and treated at the Dana-Farber Cancer Institute (DFCI) were reviewed. The end date of 2007 was chosen to ensure at least 4.5 years of potential follow-up time. Patient characteristics, histology, treatment history, and survival data were abstracted from electronic medical records. Patients were excluded if the tumor subtype was unknown, they did not have distant metastases or locally advanced disease treated with palliative intent, they did not receive any palliative chemotherapy, they did not receive at least one line of palliative chemotherapy at DFCI, they had another active malignancy, or they had more than one breast primary.

## Definitions

Breast cancer subtypes were classified as HR<sup>+</sup> (estrogen receptor [ER]-positive or progesterone receptor [PR]-positive and HER2 nonamplified), TNBC (HR<sup>-</sup>, HER2 nonamplified), or HER2-amplified (immunohistochemistry score of 3+, fluorescence

in situ hybridization amplification  $\geq 2.0$ , or both; HR<sup>+</sup>, or HR<sup>-</sup>). ER and PR status were classified as abstracted from pathology reports according to the classification applicable at diagnosis.

The duration of chemotherapy of each line was defined as the initiation of one chemotherapy regimen to the initiation of the next line of therapy as a result of disease progression or toxicity. The term *chemotherapy* may refer to traditional chemotherapy or a clinical trial therapy. Endocrine monotherapy and vaccine trials were excluded. Details on what constituted a line of chemotherapy and how the duration was calculated is outlined in Appendix A (available online, in this article, at JNCCN.org).

This study was approved and performed according to the guidelines of the DFCI Institutional Review Board.

## Statistical Analysis

Descriptive statistics were used to summarize patients' demographic and clinical characteristics. Fisher exact tests were used to examine categorical variables and Kruskal-Wallis tests were used to examine continuous variables between the subtypes. All *P* values presented are 2-sided; a *P* value of less than 0.05 was considered significant.

Overall survival and duration of chemotherapy were calculated using the Kaplan-Meier method. Overall survival time was defined as the time between metastatic diagnosis and death. Death was considered an event. If the patient was still alive at the time of medical record review or was lost to follow-up, overall survival was censored at the date of last entry in the medical record on which the patient was still alive. To determine the duration of chemotherapy, progression and toxicity were considered events. The line of therapy was censored if the patients were undergoing ongoing therapy at the time of medical record review; they were lost to follow-up; or did not experience progression on therapy. Patients still on treatment at time of last follow-up or who were lost to follow-up were censored on the last date of known treatment.

In determining the patterns of chemotherapy use at end of life (EOL), only patients who had died and had undergone complete follow-up were included in the analysis.

## Results

### Patient and Disease Characteristics

Of the 318 patients with MBC with complete information on ER, PR, and HER2 status, 199 patients were included for analysis (Figure 1). Of the 119 patients who were excluded, 43 did not have distant metastasis or locally advanced disease treated with palliative intent, 11 patients did not receive at least 1 line of palliative chemotherapy at DFCI, 38 patients did not receive any palliative chemotherapy, 13 patients had another active malignancy, and 14 patients had at least 2 breast primaries. Also excluded were 32 patients with HR<sup>+</sup> disease who were still receiving hormonal monotherapy with no receipt of palliative chemotherapy. The median age of these patients was 55 years old (range, 35–88). Patients who had previously received hormonal therapy and then proceeded to chemotherapy were included in the analysis. Subgroup distribution was: HR<sup>+</sup>, 48% (n=96); TNBC, 22% (n=44); and HER2<sup>+</sup>, 30% (n=59). Median follow-up was 2.4 years (range, 0.1–8.6). Median age at metastatic diagnosis was 53 years (range, 28–87).

No major differences in age, race, menopausal status, disease stage, or receipt of adjuvant/neoadjuvant chemotherapy were seen between subtypes (Table 1). As expected, histologic grade ( $P<.0001$ ), receipt of adjuvant/neoadjuvant endocrine therapy ( $P<.0001$ ), receipt of adjuvant/neoadjuvant trastuzumab therapy ( $P<.0001$ ), and disease-free interval ( $P<.0001$ ) varied between subtypes. Although no significant differences were seen in the number of metastatic sites, statistically significant differences in sites of first and subsequent metastasis were seen between the subtypes. For example, central nervous system (CNS) metastases were noted in half of the patients with either HER2-amplified or TNBC subtypes, compared with 26% of patients with HR<sup>+</sup> cancers ( $P=.0011$ ). Chest wall recurrences were noted in 32% of patients with TNBC, compared with 9% and 15% of patients with HR<sup>+</sup> or HER2-amplified tumors, respectively ( $P=.0048$ ). Bone metastases were most common in patients with HR<sup>+</sup> tumors ( $P<.0001$ ); liver metastases were more common in patients with HR<sup>+</sup> or HER2-amplified tumors, compared with patients with TNBC ( $P=.0010$ ).

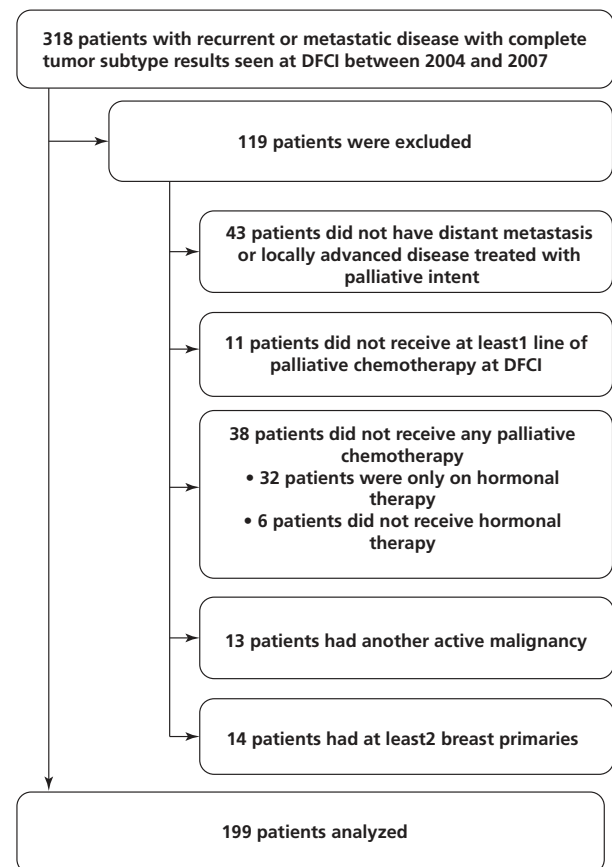
### Treatment

The most commonly used chemotherapies in the first-line setting included capecitabine, followed by

vinorelbine and paclitaxel. No major qualitative differences were seen in chemotherapy use in the first line, except for the inclusion of anti-HER2 therapy in patients with HER2-amplified disease. A total of 11, 21, and 15 patients were enrolled in clinical trials in the first, second, and third line of treatment, respectively (Appendix B, available online, in this article, at JNCCN.org).

Patients with HER2-amplified MBC received more lines of chemotherapy than patients with other subtypes ( $P=.0320$ ). In addition, the proportion of patients receiving chemotherapy by line was consistently similar or higher in HER2-amplified tumors compared with other subtypes (Figure 2). For example, nearly 60% of patients with HER2-amplified tumors were treated with fourth-line chemotherapy, compared with approximately 40% of patients with HR<sup>+</sup> or TNBC tumors.

The duration of chemotherapy received by patients also differed by subtype, with a trend for pa-



**Figure 1** Patients excluded from analysis.  
Abbreviation: DFCI, Dana-Farber Cancer Institute.

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**Table 1 Patient, Disease, and Treatment Characteristics by Tumor Subtypes**

	Total	HR <sup>+</sup>	TNBC	HER2 <sup>+</sup>	P Value
Number of patients (%)	199	96 (48)	44 (22)	59 (30)	
<b>Median Age (range)</b>					
Initial diagnosis	49 (26–83)	50 (27–81)	48 (28–73)	49 (26–83)	.3692
Metastatic diagnosis	53 (28–87)	54 (30–84)	49 (28–75)	52 (29–87)	.2332
<b>Race (%)</b>					
White	184 (92)	88 (92)	40 (91)	56 (95)	.9115
Black	8 (4)	4 (4)	2 (5)	2 (3)	
Others	7 (4)	4 (4)	2 (5)	1 (2)	
<b>Menopausal Status (%)</b>					
Premenopausal	107 (54)	55 (57)	21 (48)	31 (53)	.4680
Postmenopausal	90 (45)	41 (43)	22 (50)	27 (46)	
Unknown	2 (1)	0 (0)	1 (2)	1 (2)	
<b>Stage at Initial Presentation (%)</b>					
1	18 (9)	8 (8)	4 (9)	6 (10)	.0981
2	68 (34)	35 (37)	14 (32)	19 (32)	
3	55 (28)	21 (22)	20 (46)	14 (24)	
4	57 (29)	31 (32)	6 (14)	20 (34)	
Missing	1 (1)	1 (1)	0 (0)	0 (0)	
<b>Grade (%)</b>					
1	13 (7)	12 (13)	0 (0)	1 (2)	<.0001
2	62 (31)	43 (45)	5 (11)	14 (24)	
3	118 (59)	37 (39)	38 (86)	43 (73)	
Unknown	6 (3)	4 (4)	1 (2)	1 (2)	
<b>Neoadjuvant Therapy (%)</b>					
Yes	37 (26)	14 (21)	11 (29)	12 (31)	.7466
No	104 (73)	50 (77)	27 (71)	27 (69)	
Missing	1 (1)	1 (2)	0 (0)	0 (0)	
<b>Adjuvant/Neoadjuvant Chemotherapy (%)</b>					
Yes	122 (86)	53 (82)	35 (92)	34 (87)	.5890
No	19 (13)	11 (17)	3 (8)	5 (13)	
Missing	1 (1)	1 (2)	0 (0)	0 (0)	
<b>Adjuvant/Neoadjuvant Endocrine Therapy (%)</b>					
Yes	80 (56)	58 (89)	0 (0)	22 (56)	<.0001
No	61 (43)	6 (9)	38 (100)	17 (44)	
Missing	1 (1)	1 (2)	0 (0)	0 (0)	
<b>Adjuvant/Neoadjuvant Anti-HER2 Therapy (%)</b>					
Yes	14 (10)	0 (0)	0 (0)	14 (36)	<.0001
No	127 (89)	64 (100)	38 (100)	25 (64)	
Missing	1 (1)	0 (0)	0 (0)	0 (0)	

Abbreviations: HR, hormone receptor; MBC, metastatic breast cancer; TNBC, triple-negative breast cancer.

## Duration of Chemotherapy in Metastatic Breast Cancer

**Table 1 Patient, Disease, and Treatment Characteristics by Tumor Subtypes (cont.)**

	Total	HR <sup>+</sup>	TNBC	HER2 <sup>+</sup>	P Value
<b>Median Time Points, mo (95% CI)</b>					
Disease-free interval (excluding stage IV)	33 (11–103)	46 (11–110)	22 (6–65)	32 (16–104)	<.0001
Overall survival since metastatic diagnosis	32 (27–41)	36 (28–49)	17 (10–22)	54 (31–66)	<.0001
<b>Sites of Metastasis at Initial MBC Diagnosis (%)</b>					
Central nervous system	9 (5)	4 (4)	3 (7)	2 (3)	.7430
Liver	98 (49)	47 (49)	18 (41)	33 (56)	.3306
Lung	63 (32)	22 (23)	20 (46)	21 (36)	.0205
Bone	116 (58)	69 (72)	18 (41)	29 (49)	<.0001
Lymph node	119 (60)	57 (59)	31 (70)	31 (53)	.1880
Chest wall	20 (10)	5 (5)	9 (20)	6 (10)	.0275
Others	78 (39)	41 (43)	16 (36)	21 (36)	.6390
Number of sites at MBC diagnosis (range)	3 (1–6)	3 (1–6)	3 (1–5)	2 (1–5)	.6385
<b>Sites of Metastasis at Last Evaluation (%)</b>					
Central nervous system	78 (39)	25 (26)	22 (50)	31 (53)	.0011
Liver	151 (76)	81 (84)	24 (55)	46 (78)	.0010
Lung	97 (49)	43 (45)	26 (59)	28 (48)	.2918
Bone	140 (70)	80 (83)	23 (52)	37 (63)	<.0001
Lymph node	140 (70)	63 (66)	38 (86)	39 (66)	.0247
Chest wall	32 (16)	9 (9)	14 (32)	9 (15)	.0048
Others	131 (34)	69 (72)	24 (55)	38 (64)	.1360
Number of sites of metastasis at last evaluation (range)	4 (1–8)	4 (1–8)	4 (1–8)	4 (1–8)	.6869
<b>Number of Lines of Chemotherapy (Range)</b>	3 (1–11)	3 (1–11)	3 (1–8)	4 (1–11)	.0320
<b>Vitals (%)</b>					
Dead	165 (83)	82 (86)	40 (91)	43 (73)	.0445
Alive or unknown <sup>a</sup>	34 (17)	14 (15)	4 (9)	16 (27)	

Abbreviations: HR, hormone receptor; MBC, metastatic breast cancer; TNBC, triple-negative breast cancer.

<sup>a</sup>Vitals were unknown for 1 patient with HR<sup>+</sup>, 1 patient with TNBC, and 2 patients with HER2<sup>+</sup> disease.

tients with HER2-amplified tumors receiving longer durations of chemotherapy. The median duration of chemotherapy in patients with HER2-amplified tumors remained at 4 months or more even out to sixth-line therapy. Patients with TNBC tended to receive the shortest duration of chemotherapy for every line of therapy (Figure 3). For patients with HR<sup>+</sup> disease, the median time between MBC and first chemotherapy was 6.0 months (range, 0–76.9) and the median number of lines of hormonal therapy was 1 (range, 0–3). The proportion of patients with HER2-amplified tumors on chemotherapy for 3 months or more was consistently higher than that of patients with TNBC tumors (Table 2). A cutoff of 3 months was chosen as a proxy for clinical benefit, assuming that most patients would be restaged in this interval. The results

were similar using a 6 month cutoff, which would be consistent with the definition of clinical benefit used in many clinical trials (Appendix B, available online, in this article, at JNCCN.org).

### Overall Survival

The median overall survival from metastatic diagnosis for the entire cohort was 32 months. Overall survival time was longest in patients with HER2-amplified disease, followed by HR<sup>+</sup> and then TNBC disease (54 vs 36 vs 17 months, respectively;  $P < .0001$ ; Table 1 and Figure 4). When patients with HER2-amplified disease were further broken down into HR<sup>+</sup> and HR<sup>-</sup> disease, the median overall survival time was 53.1 (n=31) and 55.8 months (n=28), respectively. When the median time between the ini-



tiation of chemotherapy and death was calculated, the time was 41.3 months for HER2-amplified disease, 18.9 months for HR<sup>+</sup> disease, and 13.4 months for TNBC.

### Chemotherapy at EOL

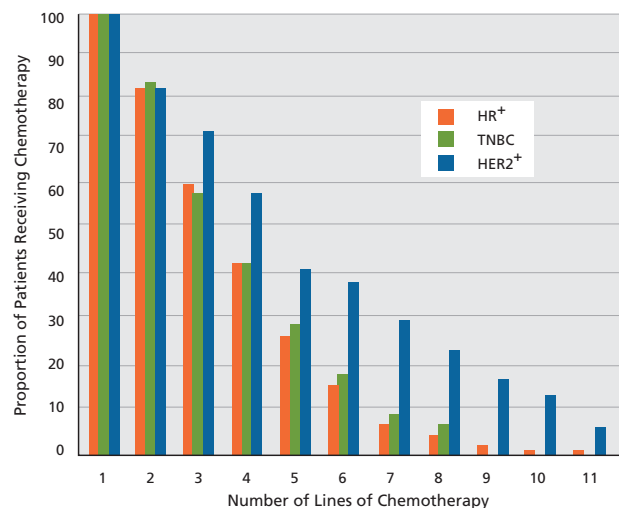
At the time of chart review, 165 of the 199 patients had died. Fourteen patients who had died but were lost to follow-up (n=14) were excluded in this analysis. The median length of time between the last date of chemotherapy and death was 37 days. No statistically significant differences were seen between the subtypes ( $P=.3280$ ; Table 3). Of the 151 patients who died and underwent complete follow-up, 27 (18%) received chemotherapy within the last 14 days of life.

### Discussion

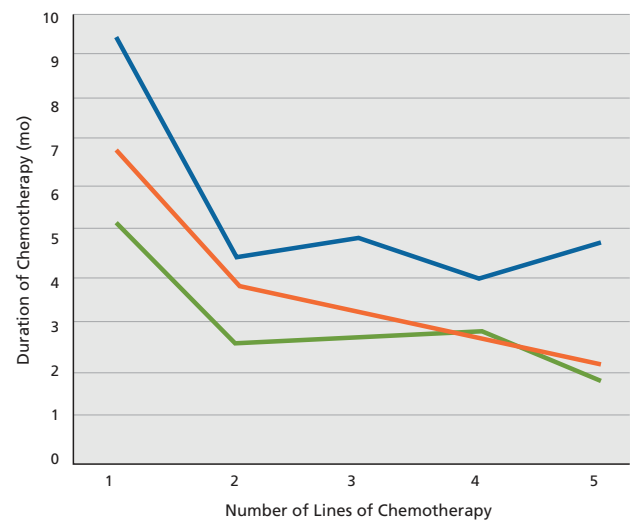
A retrospective review was conducted of patients with MBC in a single academic institution between 2004 and 2007, describing chemotherapy patterns among patients with 3 common clinical breast cancer subtypes. Patients with HER2-amplified disease were found to receive the most lines and the longest duration of chemotherapy for each line. In contrast, patients with TNBC received fewer lines of chemotherapy, and also tended to have the shortest duration of chemotherapy for each line. Patients with HER2-amplified tumors also experienced the longest overall survival. Finally, the median time from last chemotherapy administration until death was found

to be 37 days, with 18% of patients receiving chemotherapy within the last 14 days of life.

Inadequate evidence currently exists to guide patients and clinicians regarding when to consider later lines of chemotherapy and the likely outcomes of such treatment. The literature suggests that prolonged first-line chemotherapy, and even second-line chemotherapy, is associated with longer overall and progression-free survival.<sup>18,24</sup> A phase III study of eribulin versus treatment of provider choice in the third line and beyond setting showed a 2.5-months survival advantage for eribulin, indicating that later lines of chemotherapy can extend survival in some patients.<sup>19</sup> In phase II studies of trastuzumab emtansine (TDM1) in highly refractory patients with HER2-amplified MBC (median of 7 lines of palliative chemotherapy), prolonged responses were observed in a high proportion of patients.<sup>25</sup> Moreover, responses to anti-HER2 therapy can be demonstrated even after progression through TDM1.<sup>26</sup> On the other hand, the NCCN Clinical Practice Guidelines



**Figure 2** Number of lines of chemotherapy by line and subtype. Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



	Number of Patients				
	First line	Second line	Third line	Fourth line	Fifth line
HR <sup>+</sup>	96	80	59	41	26
TNBC	44	37	26	19	13
HER <sup>+</sup>	59	49	43	35	25

**Figure 3** Median duration of chemotherapy according to line and subtype. Only data up to the fifth line of chemotherapy is presented as the number of patients by subtype in the sixth line and beyond is too small (<10 patients in the TNBC category) to draw any conclusions. Of the 33 patients who received first- but not second-line therapy, 14 died after first-line treatment, 7 were lost to follow-up, and 12 had not experienced progression and/or switched to endocrine treatment. Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

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**Table 2** Proportion of Patients on Chemotherapy for More than 3 Months by Line and Subtype

Line of Chemotherapy	Number of Patients	Number of Patients on Chemotherapy for $\geq 3$ Months				P Value
		Total	HR <sup>+</sup>	TNBC	HER2 <sup>+</sup>	Fisher Exact Test
Third	128	69 (53.9%)	30 (50.9%)	10 (38.5%)	29 <sup>a</sup> (67.4%)	.0518
Fourth	95	48 (50.5%)	18 (43.9%)	8 (42.1%)	22 (62.9%)	.2035
Fifth	64	31 (48.4%)	9 (34.6%)	3 (23.1%)	19 (76.0%)	.0016
Sixth	46	26 (56.5%)	7 (46.7%)	1 (12.5%)	18 (78.3%)	.0032

Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

in Oncology for Breast Cancer<sup>27</sup> recommend supportive therapy only for patients who do not experience a tumor response to 3 sequential chemotherapy regimens.

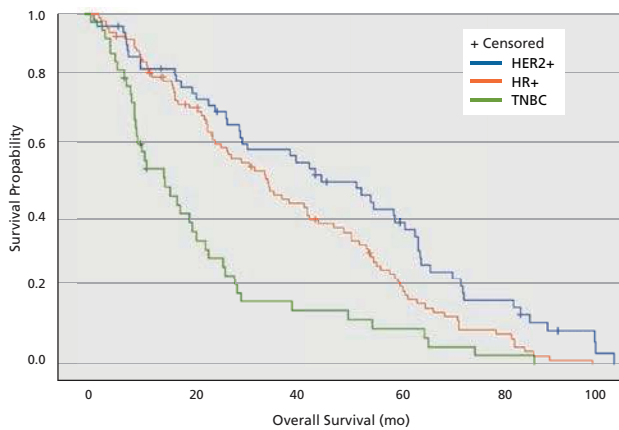
In this study, the proportion of patients receiving later lines of chemotherapy declined more rapidly in patients with HR<sup>+</sup> or TNBC tumors compared with patients with HER2-amplified tumors. In addition, the proportion of patients on chemotherapy for 3 months or more actually increased in patients with HER2-amplified disease with later lines of therapy, but decreased with each line in patients with HR<sup>+</sup> and those with TNBC. For example, only 13 of 44 (30%) of patients with TNBC were treated with fifth-line chemotherapy and, among those treated, only 3 of 13 (23%) remained on therapy for 3 months or more. In contrast, 19 of 25 (76%) patients with HER2-amplified MBC received fifth-line chemotherapy for at least 3 months. Although the numbers in each line and category are small and should be interpreted with caution, these results suggest that, compared with other subtypes, patients with HER2-amplified disease benefit differentially from later lines of therapy.

Of the limited studies analyzing only patients with MBC, Kennecke et al<sup>28</sup> showed that breast cancer molecular subtypes are associated with differences in survival after relapse. The median time from metastasis to death was 2.2 years for luminal A, 1.6 years for luminal B, 1.3 years for luminal/HER2-amplified, 0.7 years for HER2-amplified, 0.5 years for basal-like, and 0.9 years for triple-negative nonbasal breast cancers. Brown et al<sup>29</sup> found similar results in patients with stage 3–4 disease, with patients with

TNBC having the worst survival, followed by patients with ER-/PR-/HER2<sup>+</sup> disease and other breast cancers (median survival, 2.3 vs 3.6 vs 4.8 years, respectively). Interestingly, in the present study, patients with HER2-amplified disease were found to experience the longest median survival time at 4.5 years, followed by patients with HR<sup>+</sup> disease at 3.0 years and those with TNBC at 1.4 years ( $P < .0001$ ). When the HER2-amplified group was further separated according to HR, the median overall survival time was 4.4 years for HR<sup>+</sup> and 4.7 years for HR<sup>-</sup> disease. This discrepancy may be explained by the differences in treatments. The study by Kennecke et al<sup>28</sup> predated the widespread use of trastuzumab in HER2-amplified patients. Brown et al<sup>29</sup> included patients with stage III disease in their study. The present study included patients who were diagnosed with MBC between 2004 and 2007, when targeted biologic agents such as trastuzumab and lapatinib were widely used. Notably, the present study's survival estimates for patients with HR<sup>+</sup> MBC should be interpreted with some caution, because it excluded patients who did not receive chemotherapy ( $n=32$ ) but may have been undergoing an extended duration of endocrine therapy and therefore may have experienced better survival outcome. Nevertheless, the present authors believe their results clearly show improvement in survival among patients with HER2-amplified MBC compared with historical controls. They also find it notable that these improvements occurred even in the setting of a very high rate of CNS metastasis (53%).

Finally, the authors found that, despite the expected decrease in the proportion of patients re-

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**Figure 4** Kaplan-Meier curves for overall survival by subtype from the date of metastatic breast cancer diagnosis. Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

ceiving successive lines of chemotherapy, 18% were treated with chemotherapy within the last 14 days of life. This finding is comparable to that noted in a cohort of 19,000 commercially insured patients with cancer, approximately 17% of whom were still being treated within 2 weeks of death.<sup>30</sup>

ASCO has created the Quality Oncology Practice Initiative, which has identified chemotherapy cessation in the last 2 weeks of life as one of the benchmarks for improving clinical practice for patients at EOL. In practice, finding the right balance between the appropriate therapy and overly aggressive therapy is challenging. The present authors plan to expand on this work in the future to understand whether there are modifiable factors that could increase the use of hospice and reduce the use of chemotherapy at EOL.

The present study has several limitations. First, it is a relatively small study of patients in a single academic institution, and therefore may not be generalizable to the general community. In an ideal situation, prospectively collected data would be used from large groups of patients treated in both academic and community settings with equal access to treatment options. However, these data are rare. In the absence of this information, retrospective studies provide a pragmatic source of information. Second, the authors did not formally assess the response rates of each line of therapy. They chose not to do this because patients were staged at varying intervals, and clinical radiology reports do not typically adhere to RECIST requirements.

For this reason, the authors used whether the patient was on chemotherapy for 3 or more or 6 or more months as a surrogate marker of clinical benefit. Third, this study only included patients who received chemotherapy. Thus, patients with HR<sup>+</sup> tumors who were still on hormonal monotherapy at the time of analysis were excluded, and this could have biased the survival estimates toward a shorter survival. In addition, the authors did not perform a comprehensive analysis of the disease, physician, or patient factors that were associated with use of later lines of chemotherapy. The authors stress that their descriptions of the duration of later lines of chemotherapy are based only on patients who received chemotherapy. Hence, the fact that patients with HER2-amplified MBC in this study were able to remain on later lines chemotherapy for prolonged durations should not be interpreted to mean that all patients with HER2-amplified MBC should receive multiple lines of chemotherapy. Both physicians and patients likely made decisions about chemotherapy use based on multiple factors, including prior response to treatment, toxicities, disease burden, organ function, performance status, and personal preference. Finally, subtypes were based on the assessment provided at the time of diagnosis, and central pathologic review of the tumor samples was not conducted. However, all samples were reviewed for clinical purposes, as is the standard at DFCI. In addition, the authors calculated the number of lines of therapy for patients with HER2-amplified HR<sup>+</sup> (median, 3 lines of chemotherapy) and HER2-amplified HR<sup>-</sup> disease (median, 6 lines of chemotherapy). However, the numbers in each of these groups were small ( $n=31$  and  $n=28$ , respectively), and definitive conclusions about the impact of HR status on the number and duration of chemotherapy cannot be drawn.

### Implications

The emergence of targeted therapies has created a divergence regarding what was previously considered a single disease. This and other studies clearly show that the natural history and progression of MBC differ according to subtypes. Tumor subtype should be taken into consideration when planning additional lines of therapy. Traditionally, the literature supports patients with MBC to have up to 3 lines of therapy.<sup>21</sup> The present data show that a substantial proportion of patients with HER2-amplified disease undergo



## Duration of Chemotherapy in Metastatic Breast Cancer

**Table 3** Chemotherapy Patterns at the End of Life

	Total	HR <sup>a</sup>	TNBC	HER2 <sup>a</sup>	P Value
Number of patients who died <sup>a</sup>	151	74	38	39	
Median time between last chemotherapy and death, d (range)	37 (2–1384)	37 (2–354)	32 (2–385)	55 (5–1384)	.3280
Number of patients receiving chemotherapy in the last 14 days of life (%)	27 (18)	12 (16)	7 (18)	8 (21)	.8551

Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

<sup>a</sup>Of the 165 patients who died, 14 were lost to follow-up and were not included in this analysis.

therapy for a prolonged period, often receiving fourth or subsequent lines of chemotherapy. Although ongoing HER2-directed therapy after progression is fairly standard in the United States, these results may hold important implications for countries with more restrictive policies on the use of trastuzumab beyond progression.<sup>31–33</sup>

The decision when to stop chemotherapy at EOL is a complex issue.<sup>34–36</sup> Many patients undergoing palliative chemotherapy may not comprehend that it is unlikely to be curative, and this may affect their capacity to make informed decisions about when to stop treatment.<sup>37</sup> Previous groups have attempted to determine stopping rules for chemotherapy for patients with MBC, and to define the limits of treatment.<sup>36,37</sup> Despite this, chemotherapy continues to be used in patients with advanced cancer. In the present study, no statistically significant differences were seen in time between the last chemotherapy and death among the subtypes. Future studies should be considered to determine factors that may increase the interval between the last chemotherapy and death, and factors that may improve quality of life at EOL.

## Conclusions

This retrospective study showed variability in the number of lines and duration of chemotherapy and overall survival from metastatic diagnosis according to tumor subtype. These findings may have implications on the management of palliative chemotherapy, and affirm the benefits of ongoing HER2-directed therapy beyond first-line palliative chemotherapy.

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