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Original Article ONCOLOGY

Impact of progression sites and line of therapy on survival outcomes in patients with HER-2 positive metastatic breast cancer treated with T-DM1

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ABSTRACT

OBJECTIVE: Ado-trastuzumab emtansine (T-DM1) is a key treatment for HER2-positive metastatic breast cancer (HER2+ MBC), yet the influence of progression sites and therapy lines on outcomes remains unclear.To assess the relationship between progression sites and the line of T-DM1 therapy with survival outcomes in HER2+ MBC.

METHODS: We retrospectively analyzed 123 patients with HER2+ MBC treated with T-DM1. Data on metastatic progression sites (brain, liver, bone, lung, lymph nodes), line of T-DM1 therapy (2nd-line vs ≥3rd-line), and death status were examined. Due to limited survival time data, mortality was used as the primary outcome. Death rates were compared across subgroups using descriptive statistics.

RESULTS: Brain and lung progression were associated with the highest mortality rates (76.7% and 73.1%, respectively). Liver and bone progression also showed elevated death rates (70.0% and 64.3%). Notably, more patients who used T-DM1 as the second-line therapy had a higher mortality rate at 66.7% compared to those treated with it in the third line or after (45.1%).

CONCLUSION: Progression to brain and lung during T-DM1 treatment correlates with higher mortality. Early-line use of T-DM1 may be linked with worse outcomes, possibly due to more aggressive disease biology. The obtained data could inform the decision-making process when treating patients with HER2+ MBC and predict their prognosis.

Keywords: Ado-trastuzumab emtansine; brain metastases; HER2-positive breast cancer; liver metastases; metastatic progression; therapy line.

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Approximately 15 to 20 percent of cases of breast cancer are HER2+ or have aggressive tumor biology and poor disease outcomes but are responsive to targeted therapies. Her2-directed therapies have completely changed the prognosis of HER2+ MBC, with the patients getting more life years and better outcomes for the disease [1]. Considering its use in the management of HER2+ MBC, ado-trastuzumab emtansine (as T-DM1), T-DM1 is especially important.

The drug T-DM1 detects a trastuzumab and cytotoxic emtansine (DM1) combination in an antibody-drug conjugate configuration, thereby enabling targeted chemotherapy to predominantly affect HER2-expressing cancer cells [1]. Its experience in the second line setting has been backed by the EMILIA trial, though it is commonly used in the subsequent training, third line, or later. Although patients widely use T-DM1, response to the drug varies based on different clinical situations. The number of residual diseases, the types of past therapies, and specific locations of cancer spread contribute to the fact that prognosis and effectiveness of treatment can be patient-specific.

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The location at which the disease advances during T DM-1 treatment may strongly affect survival. Brain metastases are prevalent in HER2+ MBC— affecting up to 30–50% of patients during their disease course — and associated with impaired quality of life and survival [2]. Similarly, the invasion of disease into internal organs, such as the liver or lungs is a usual occurrence of advanced illness and poorer health outcomes. However, real-world data exploring how the site of disease progression affects survival in patients treated with T-DM1 is still quite limited. Timing the administration of T-DM1 differently along the sequence of treatments could also affect overall survival. The advantages of T-DM1 in the second-line situation have been well established in trials, but in everyday life T-DM1's benefit to initiate before versus after that stage remains unclear. Early initiation of T-DM1 may possibly signify a more aggressive disease, and, similarly, a late initiation could possibly reflect increased treatment resistance. Determinants of whether survival is affected by the line of t-DM1 therapy may also be used to inform the planning of personalized treatment strategies.

The main purpose of this study is to find out whether the location where the disease progresses and the stage of therapy can influence overall survival in HER2+MBC patients treated with T-DM1. Our aims involve the establishment of whether disease progression at critical metastatic areas such as the brain, liver, bones, lung, as well as distant lymph nodes is associated with higher mortality. and investigate survival outcome differences with reference to T-DM1 initiation as second, third, or later-line therapy [2]. Lacking sufficient time-to-event data among our participants, we decided to analyze survival by observing death status – our binary outcome.

Analysis of such associations can help clinicians to identify at-risk populations and design better therapeutics. The finding of the present report takes on additional value in the age of personalized oncology, where decisions on therapy are driven by data. Through new considerations of T-DM1's effectiveness, our work adds value to prognostic models predictive of those with HER2+ metastatic breast cancer.

Highlight key points

- Brain and lung metastases were the strongest predictors of mortality during T-DM1 therapy.
- Second-line use of T-DM1 showed higher mortality than later use, suggesting more aggressive disease.
- Progression site and therapy line are key factors for prognosis and treatment planning.
- Findings highlight the need for prospective studies to validate real-world outcomes.

MATERIALS AND METHODS

Study Design and Population

As a retrospective, observational study the aim was to analyze the relationship between locations of metastatic progression and therapy line and its influence on survival in HER2 positive metastatic breast cancer (HER2+ MBC) patients treated by ado-trastuzumab emtansine (T-DM1). The study recruited women diagnosed with HER2 + MBC, and who had undergone T-DM1 treatment at any point in therapy. Analysis of the institutional records between [insert date range] saw 123 patients qualify for inclusion in the study.

Data Collection

Institutional records processed in an anonymized database served as the data for analysis. To carry out the study, data on the characteristics of patients; metastatic sites during T-DM1 treatment; therapeutic line introducing T-DM1, and overall survival were gathered. Specific evaluation of progression at the following sites was made:

- Brain
- Liver
- Bone
- Lung
- Distant lymph nodes

Each variable determined whether a particular site had progressed during T-DM1 treatment; 0 for no progression and 1 for progression.

Treatment sequencing data were used to create two line-of-therapy groups: 2nd-line or later; and 3rd-line or later. Total mortality (binary variable 1=dead, 0=alive) was the main outcome measure. Because overall survival (OS) and progression-free survival (PFS) were recorded as time-to-event variables in the dataset and were highly incomplete, these measures were not included in the final analysis.

Statistical Analysis

This study was approved by the Kartal Dr. Lutfi Kirdar City Hospital Ethics Committee (Approval No: 2025/010.99/1619, Date: 27.05.2025).

TABLE 1. Mortality by progression site

Progression site	Progression	Patients (n)	Deaths (n)	Death rate (%)
Brain	Yes	30	23	76.7
	No	50	23	46.0
Lung	Yes	26	19	73.1
	No	54	27	50.0
Liver	Yes	20	14	70.0
	No	60	32	53.3
Bone	Yes	28	18	64.3
	No	52	28	53.8
Lymph nodes	Yes	17	8	47.1
	No	61	37	60.7

Descriptive statistics gave an overview of more or less how often each site of progression, therapy line, and death status occurs. The primary consideration was the comparison of death rates for patients by progression sites and lines of therapy. For all variables, we calculated the occurrence and percent of the number of patients who died. Numberically the death rates were indicated in tabular structure and graphically with bar charts.

Patients were grouped based on:

- There was progression at all metastatic sites or none at all.
- Stage of therapy (initial second line of therapy vs. later lines).

Because data was categorical and time-to-event information was unavailable, inferential statistical procedures such as Chi-square or logistic regression were not focalized. Therefore, the analysis focused on representing not only mortality trends with the help of tables but also in graphical forms.

All statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

The analysis included a cohort of 123 HER2-positive metastatic breast cancer (HER2+ MBC) patients receiving treatment with ado-trastuzumab emtansine (T-DM1). From the total, 100 patients provided adequate survival information and were included in the primary outcome analysis. Data for metastatic progression sites were available for ranges of 88–91 patients, with a line of therapy noted for 108 patients, contingent upon the site.

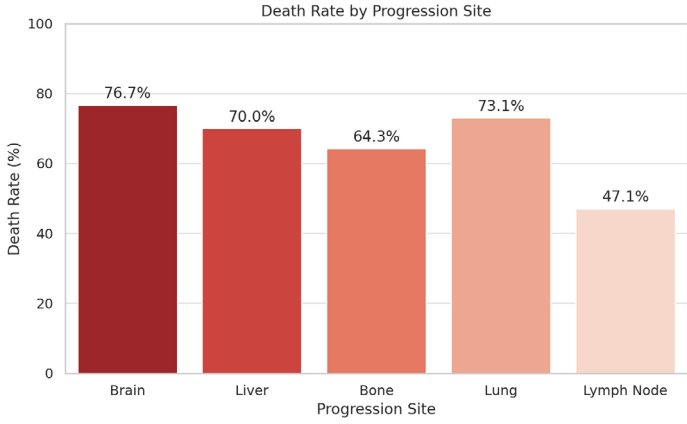

FIGURE 1. Death rate by progression site.

Among patients with a recorded sequence of their treatment, 39 (36.1%) received T-DM1 forth time. For the remainder, data regarding their treatment sequence either were missing or were not adequately defined.

Mortality by Metastatic Progression Site

Survival outcomes among the patients were significantly varying based on where their disease progressed first during T-DM1 therapy. The highest mortality rates were observed for the patients with metastases to the brain or lungs, while patients with metastases in the liver or bones were at lower mortality risk. Lymph node progression was correlated with the lowest death rates among the patients.

Figure 1 which is the Death Rate by Progression Site represents a breakdown of patients who died of their respective diseases in relation to the location where they progressed during a T-DM1 treatment: brain, liver, bone and lung, and distant lymph nodes.

Table 1. Mortality by Progression Site. A much greater percentage of patients died (76.7% with brain metastasis and 73.1% with lung metastasis), which could indicate that T-DM1 is less effective or that the underlying disease biology is more advanced when metastasis occurs in these areas.

Mortality by Line of Therapy

The in-patient death rate for patients undergoing T-DM1 in second-line therapy (66.7%) was higher than in the third-line or further periods (45.1%).

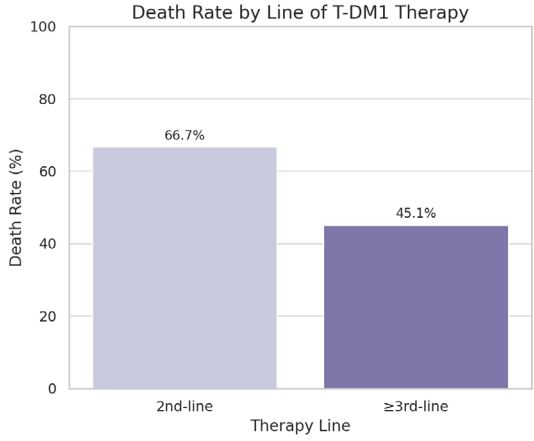

FIGURE 2. Death rate by line of therapy.

TABLE 2. Mortality by line of therapy

T-DM1 therapy line	Patients (n)	Deaths (n)	Death rate (%)
2nd-line	39	26	66.7
≥3rd-line	51	23	45.1

Figure 2. Death Rate by Line of Therapy. According to the data, 66.7% of patients receiving second-line T-DM1 died, whereas only 45.1% of those who started the treatment were in third or later lines.

Table 2. Mortality by Line of Therapy may be explained by the tumor aggressiveness: the patients with more aggressive disease were treated earlier with T-DM1 and there was a paradoxical higher death rate in the second-line group.

DISCUSSION

Here, the study addressed the interplay between metastatic progression sites, T-DM1 treatment sequence, and mortality among patients with HER2-positive metastatic breast cancer. Our findings suggest that progression to the brain and lungs during T-DM1 treatment is associated with markedly higher mortality, while the timing of T-DM1 therapy—whether administered in the second line or third line and beyond—may influence survival outcomes in ways that challenge prior assumptions derived from clinical trials.

The relationship between the progression of CNS disease and high mortality (76.7%) underscores the difficulties clinicians experience treating metastatic breast cancer that is HER2 positive. For patients with advanced HER2-positive disease, up to 50%, of brain metastases develop, and brain metastases management is still a major clinical challenge. Even with systemic effectiveness, poor CNS penetration of T-DM1 suggests that it may not be as effective against intracranial disease. Research by Montemurro et al. [3–5] revealed that T-DM1 has reduced effectiveness among untreated or growing brain metastase cases with pronounced exceptions where selected CNS responses are seen [3]. Our data reinforce the notion that patients with CNS involvement represent a high-risk subgroup and may benefit from alternative or combinatorial strategies involving CNS-active agents such as tucatinib or neratinib.

Along the same lines, the high mortality rate, 73.1%, in patients with lung involvement becomes additional evidence of the aggressive character of visceral metastases. Having lung disease with a significant tumor load and rapid progression concurrent with lung disease may cause pulmonary dysfunction and increase patient morbidity. As expected, patients with liver (70.0%) or bone (64.3%) metastases also had increased mortality rates, with the trend being less pronounced. This is consistent with published data noting the substantial correlation between metastatic spread to the visceral organs and unfavorable survival in patients with breast cancer [6, 7]. T-DM1 continues to be effective for visceral and non-visceral metastatic disease, although its clinical benefits might be blunted in those with advanced organ involvement especially when associated with poor overall health or prior resistance to treatment.

Contrastingly, lymph node progression did not confer a worse prognosis in our dataset. In fact, patients with nodal involvement exhibited a lower mortality rate (47.1%) compared to those without (60.7%). While this may seem counterintuitive, it is consistent with the hypothesis that isolated nodal progression represents a more indolent form of metastatic disease. Because the lymph nodes are usually amenable to local therapy and do not quickly impair the function of major organs, this mode of spread implies a more favorable short-term prognosis. This finding needs further study, particularly in light of increased treatment strategies focusing on oligometastatic disease such as stereotactic body radiation [8].

One of the most provocative findings of this study was the higher observed mortality among patients who

received T-DM1 as second-line therapy compared to those treated in later lines (66.7% vs. 45.1%). This result contradicts the results of the EMILIA trial in which T-DM1 used as second-line treatment was associated with a clear survival benefit, as compared to lapatinib and capecitabine [1]. There are a number of feasible reasons for this surprising result. First, confounding by indication is likely at play: patients who received T-DM1 earlier may have done so due to rapid progression on first-line therapy, indicating more aggressive disease biology. Second, there is a possibility that selection bias is tilted toward T-DM1 usage in sicker patients or those who are unable to tolerate other treatments. Third, because the inclusion of patients in everyday clinical practice when they are in worse health status, with underlying conditions, or have reasons to avoid some treatments is present, differences in clinical trial outcomes are established.

Additionally, among patients who received T-DM1 in the third-line setting or later, the second-line treatments administered before initiating T-DM1 included a combination of pertuzumab and trastuzumab with a taxane (docetaxel or paclitaxel) in most cases. A smaller subset had received dual HER2 blockade followed by capecitabine-based regimens. This sequence reflects evolving treatment landscapes where newer agents such as trastuzumab deruxtecan or tucatinib were either not accessible or reserved for later stages. These observations suggest that prior exposure to standard HER2-directed regimens might influence the efficacy of subsequent T-DM1 therapy. However, due to the retrospective nature of this study and the heterogeneity of treatment strategies, we recommend cautious interpretation of these sequences. Future studies with detailed therapy mapping and temporal analysis will help clarify the effect of prior regimens on T-DM1 outcomes.

Treatment sequencing might also contribute to these differences. Novel therapies at some medical centers such as trastuzumab deruxtecan or tucatinib along with capecitabine are saved for the following lines of treatment especially when T-DM1 had been previously efficacious. The limited access to the less frequent use of newly introduced therapies in specific environments would skew the results of survival analysis, making it pillow to precisely determine how the order of treatment influences therapeutic benefit [9]. Overall, our findings show that the process of establishing treatment order in HER2+ MBC is sophisticated because it contemplations clinical standards, tumor progression, health state, and therapeutic options.

Our findings can further enlarge the current evidence base on how T-DM1 performs in clinical practice outside the clinical setting. Observational studies such as ours are still essential for confirming efficacy, and controlled studies continue to be vital for establishing efficacy, but observational studies can also provide light on how treatment works in different and representative populations [10, 11]. Through this, they create visibility on ignored challenges – like insufficient CNS treatment or sub-optimal schedules – and remove the discussion over mitigating important research questions.

Although our findings prove to be helpful we have to keep in mind that our study has limitations. Lack of access to precise time-to-event statistics (such as PFS and OS) was an important obstacle since it limited the use of non-parametric statistic Kaplan-Meier survival curves or multivariable Cox proportional hazards models. Consequently, survival outcomes were assessed using a binary mortality endpoint, limiting the granularity of interpretation. Moreover, our analysis failed to gather crucial clinical factors such as ECOG performance status, tumor extent, hormone receptor status, and previous treatments that may affect the interpretation of the survival outcomes. Retrospective analysis can also result in information bias, particularly with the manner in which the progression of disease is recorded. We relied on recorded binary indicators of progression rather than radiographic progression-free intervals or RECIST-based metrics [12–14]. Furthermore, treatment heterogeneity—including dose modifications, delays, and duration of T-DM1 therapy—was not captured in the current dataset.

Despite this, the study provides valuable information on how metastatic patterns and time for treatment affect the outcome in patients who are on T-DM1 therapy with HER2 + MBC. The study points out the need to individualize treatment plans for patients who experience the advancement of central nervous system or visceral disease and questions the possible prognostic value of CD-DM1 treatment timing [15, 16].

Conclusion

The results of this study show the clinical relevance of metastatic locations and the use priority of treatments in HER2+ patients with metastatic breast cancer maintained on T-DM1. Among the metastatic sites assessed, progression to the brain and lungs emerged as the strongest predictors of mortality, with

death rates exceeding 70% in both groups [17]. These findings reinforce the clinical understanding that central nervous system and visceral involvement represent biologically aggressive disease states and may signal resistance to standard HER2-targeted therapies, including T-DM1.

The limited ability of T-DM1 to effectively penetrate the blood-brain barrier may partly explain its diminished efficacy in patients with CNS involvement. This underscores the urgent need to incorporate CNS-active HER2-targeted agents—such as tucatinib-based regimens—into the treatment pathway for patients at high risk for, or with established brain metastases [18]. Similarly, the poor outcomes observed with lung and liver progression highlight the need for more tailored systemic strategies and potential combinations in heavily burdened visceral disease.

Another striking result was that the use of T-DM1 as a second-line treatment showed faster mortality in patients receiving T-DM1, compared to patients who received T-DM1 in an earlier stage. Unlike data from the clinical trials, this finding is possibly swayed by real-world scenarios in that in the more aggressive conditions, more treatment escalation is likely to follow sooner.

This evidence does not support the idea that clinicians must consider the biology of the disease but also the course of patient treatment in deciding when and where to introduce such T-DM1. Future prospective studies are critical in supporting these observations and improving upon the rationale order of T-DM1 treatment in HER2+ MBC.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar Sehir Hastanesi Ethics Committee granted approval for this study (date: 27.05.2025, number: 2025/010.99/1619).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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