

**Development and responses of brain metastases during treatment with trastuzumab emtansine (T-DM1) for HER2 positive advanced breast cancer: A single institution experience**

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Word count (excluding abstract) =2810

## Abstract

**Background:** Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that does not cross an intact blood-brain barrier. In the EMILIA trial of T-DM1 versus capecitabine/lapatinib for HER2 positive advanced breast cancer, all patients had baseline brain imaging, and 9/450 (2%) of patients with negative baseline imaging developed new brain disease during T-DM1. We assessed the frequency of brain progression in clinical practice, without routine baseline imaging.

**Methods:** A retrospective study of all patients treated with T-DM1 at the Royal Marsden Hospital from 2011-2016. Data collected included baseline characteristics, previous treatment for advanced breast cancer, sites of metastatic disease, duration of T-DM1, sites of progression and treatment of CNS progression.

**Results:** Fifty-five patients were identified who had received a median of 2 prior lines of treatment (range 0-5). All were HER2 positive; 45 patients had IHC 3+ tumours and 10 were ISH positive. Patients received a median of 12 cycles of T-DM1 (range 1-34), and 6 remain on treatment at the time of analysis. Before commencing T-DM1, 16/55 (29%) had known brain metastases (treated with whole brain (9) stereotactic radiotherapy (6) or both (1)). Brain was the first site of progression in 56% (9/16) patients, with a median time to brain progression of 9.9 months (95% CI 3.9-12.2).

In patients without known baseline brain metastases, 17.9% (7/39) developed new symptomatic brain disease during T-DM1, after a median of 7.5 months (95%CI 3.8-9.6). Brain progression was isolated, with control of extra-cranial disease in 4/7 patients. Only one patient was suitable for stereotactic radiotherapy.

Median time to extra-cranial progression in all patients was 11.5 months (95% CI 9.1-17.7), and median OS in all patients was 17.8 months (95% CI 14.2-22).

**Conclusions:** In patients not screened for brain metastases at baseline, the brain was the first site of progression in a significant proportion. Baseline brain imaging may have a role in standard practice for patients commencing T-DM1 therapy.

Words=314

## Background

T-DM1 is a novel antibody-drug conjugate combining a microtubule-inhibitory agent, emtansine (a derivative of maytansine) with the anti-HER2 antibody, trastuzumab. The EMILIA trial demonstrated that response rate, median progression-free survival (PFS) and median overall survival (OS) with T-DM1 were superior to the prior standard of care, a combination of capecitabine and the dual EGFR/HER2 directed tyrosine kinase inhibitor (TKI), lapatinib, for previously treated HER2 positive advanced breast cancer [1]. T-DM1 is also superior to standard chemotherapy in patients who have received prior lapatinib [2]. The rate of CNS progression was not initially reported in either of these pivotal trials; however, CNS progression during trastuzumab is a well-described clinical problem, occurring due to the extra-cranial efficacy of the agent leading to longer survival, combined with poor penetration of the CNS. In approximately half of patients with brain progression on trastuzumab, this occurs whilst the extra-cranial disease remains controlled [3], allowing local treatment of the brain disease (with surgery and/or radiotherapy) and continuation of trastuzumab in such patients. In a retrospective analysis of the EMILIA trial, for which baseline brain imaging was mandatory, 45/495 patients randomised to T-DM1 had brain metastases, which were untreated in 30%. CNS progression occurred in only 10 of these 45 patients (22.2%), with new CNS disease reported in just 9/450 patients with no CNS disease on baseline imaging (2%) [4], potentially suggesting CNS penetration and activity of T-DM1 in patients whose disease or treatment has compromised the blood-brain barrier. A pre-clinical study has confirmed activity of T-DM1 in the brain microenvironment in trastuzumab-resistant cell cultures and mouse models [5], supporting these observations.

In routine clinical practice, brain imaging to identify asymptomatic brain metastasis is frequently not conducted. We reviewed the incidence of symptomatic brain progressions in the absence of baseline imaging, to determine the frequency and timing of symptomatic CNS progression on T-DM1 in a single institution.

## **Methods**

### **Study design**

This retrospective study was initiated with the primary objective of determining the frequency of brain progression in patients with advanced HER2 positive breast cancer receiving T-DM1. Secondary endpoints comprised the timing of brain versus extra-cranial progression, the relative frequency of parenchymal and leptomeningeal brain disease in this patient group, and the progression-free and overall survivals in the sub-groups of patients with known brain metastases, those who developed symptomatic brain disease during therapy and patients without diagnosed CNS disease.

### **Patients**

Eligible patients who received at least one cycle of T-DM1 for HER2 positive advanced breast cancer between January 1<sup>st</sup> 2011 and January 1<sup>st</sup> 2016 were identified from the Royal Marsden Hospital Pharmacy database. The data cut-off date was 13<sup>th</sup> July 2016.

Hormone receptor positive was defined as an oestrogen and/or progesterone receptor Allred score of 3/8 or greater. HER2 positive was defined as HER2 3+ positive by IHC, or an *in situ* hybridisation (ISH) ratio >2.0, or an absolute HER2 copy number of  $\geq 6$  also defined HER2 positivity regardless of ratio, as per ASCO/CAP guidelines [6]. Data were collected from the electronic patient record on gender, age, breast cancer histology, receptor status, prior treatment for advanced breast cancer, sites of disease, prior local treatment for brain metastases, number of cycles of T-DM1, best response to T-DM1, dates of brain and extra-cranial progression, type of brain progression, treatment of CNS progression and date of death or last follow-up.

Surveillance brain imaging was performed approximately every 3 months in patients with known brain metastases.

### **Statistical Methods**

In patients with and without known brain disease at baseline, time to central nervous system (CNS) progression was defined from start of treatment with T-

DM1 to date of any CNS progression. Any CNS progression-free patients were censored at last follow up.

Time to extra-cranial progression was also calculated in patients with and without CNS progression from date of 1<sup>st</sup> T-DM1 infusion to date of extra-cranial progression. Kaplan Meier methods were used to calculate time to extra cranial progression.

CNS Response rate was assessed only in patients with known CNS disease prior to commencing T-DM1. This is presented as a proportion with the 95% confidence interval. The relative frequency of parenchymal versus leptomeningeal versus mixed CNS disease developing on T-DM1 was assessed only in patients without known CNS disease prior to T-DM1.

Progression-free survival was calculated in all patients from date of 1<sup>st</sup> T-DM1 infusion to date of a) any progression and b) non-CNS progression using Kaplan-Meier methods. Overall survival was calculated from date of 1<sup>st</sup> T-DM1 infusion using Kaplan-Meier methods, surviving patients were censored at date of last follow-up.

## **Results**

Fifty-five patients were treated with T-DM1 with a median duration of follow-up of 20.5 months. Baseline demographics are summarised in table 1. The majority of patients (30/55, 54.5%) had received at least 2 prior lines of treatment for advanced breast cancer, although T-DM1 was first-line therapy in 10/55 (18.2%) who had relapsed on or within 6 months of completing adjuvant trastuzumab. Twenty-seven patients (49.1%) had received prior lapatinib, but only 8 (14.5%) had been exposed to pertuzumab, reflecting the timing of our study relative to licensing of pertuzumab in Europe in 2013. Patients received a median of 12 cycles of T-DM1 (range 1-34 cycles).

### **Patients with brain disease prior to T-DM1**

Sixteen patients (29.1%) had known brain involvement at baseline, with parenchymal metastases in all patients, one with additional leptomeningeal involvement reported on MRI. All patients had received prior local therapy to

the brain; with whole brain radiotherapy (WBRT) in 10 patients (62.5%), and stereotactic radiotherapy (RT) without WBRT in 6 patients (37.5%), of whom 2/6 also underwent neurosurgery. One of the 16 patients (6.25%) had untreated brain progression (leptomeningeal progression after prior stereotactic RT) at the time of starting T-DM1.

None of the 13 assessable patients had radiological responses in the brain to T-DM1; two patients were not assessable due to death after one cycle of T-DM1, a 3<sup>rd</sup> did not have any follow-up brain imaging during T-DM1. The brain was the first site of progression in 9/16 patients (56.3%), although two had concurrent extra-cranial progression. A further two patients developed brain progression during subsequent lines of therapy, 2 and 8 months after completing T-DM1, and a third patient died with progressive neurological symptoms with no radiological confirmation of CNS progression. Treatment for brain progression was WBRT in five of the 16 patients (31.3%), stereotactic RT in three (18.8%) and no brain-directed therapy in 8 (50%). The median time to brain progression in these 16 patients was 9.9 months (95% confidence interval (CI) 3.9-12.2 months). The median OS was 15.3 (95% CI 4.7-Not reached) months in patients with known brain disease at baseline

### **Patients without known brain disease prior to T-DM1**

The remaining 39 patients (70.9%) were not known to have brain disease on commencing T-DM1, with routine brain imaging not performed in asymptomatic patients. Three of the 39 patients had undergone an MRI brain within a month prior to starting T-DM1 to investigate symptoms, which showed no evidence of disease in all 3. During treatment with T-DM1, 7/39 patients (17.9%) developed symptomatic CNS disease, parenchymal brain metastases in 5 patients and leptomeningeal disease in 2 patients. Three of the 7 patients (42.9%) had extra-cranial progression diagnosed concurrently. Five of the 7 patients underwent WBRT (71.4%), one was suitable for stereotactic RT (14.3%) and one received no brain-directed therapy (14.3%).

A further three patients developed symptomatic brain progression, 4, 7 and 15 months respectively after completing T-DM1 for extra-cranial progression, two of whom received WBRT.

The median time to brain progression in the 7 patients without known brain disease prior to T-DM1, who then developed symptomatic CNS progression during this treatment was 7.5 months (95%CI 3.8-9.6 months). Table 2 reports the time to brain progression for patients with brain disease at baseline, compared to those who developed brain disease on T-DM1. Figure 1 shows the time to brain progression (1A) and extra-cranial progression (1B) in all patients, by baseline brain disease status. The median OS of patients who developed brain disease during T-DM1 was 12.4 (95% CI 10.5-17.8) months, compared to 22 months in patients without brain disease before or during T-DM1 (95% CI 15.1-Not reached). The median OS from diagnosis of new CNS disease was 5.7 months (95% CI 0.9-12.0).

### **CNS haemorrhage**

Three of the 23 patients (13.0%) with baseline or new brain disease developed significant intra-cranial haemorrhage associated with parenchymal brain metastases whilst on T-DM1. This was the first presentation of brain disease in one patient, and occurred within a new metastasis in the second patient who had multiple pre-treated metastases; both haemorrhages were terminal events. The third patient underwent craniotomy and removal of a previously stereotactic RT-treated parietal lobe metastasis which had become haemorrhagic, with good recovery.

### **Efficacy of T-DM1 in all patients**

At the time of analysis, 23/55 patients were alive, ten of whom remained on T-DM1. Four of 51 evaluable patients (7.8%) had a complete response to T-DM1, of whom three remain in complete remission on treatment at median 18 months follow-up; the fourth died from neurological complications of radiation necrosis. A further 14 patients had a partial response (PR), giving an overall response rate of 35.3% (95% CI: 22.4 – 49.9). Four patients were not evaluable for response due to death before response evaluation scans in 2

patients, early cessation of T-DM1 for toxicity in 1 patient and no extra-cranial disease in 1.

The median time to extra-cranial progression in all patients was 11.5 months (95% CI 9.1-17.7 months), shown in figure 2A, and median OS in all patients was 17.8 months (95% CI 14.2-22 months), figure 2B. Figure 3 shows the overall survival by brain disease status.

Figure 4 summarises CNS and extra-cranial outcomes during T-DM1.

## **Discussion**

In this single institution experience of T-DM1, without mandatory baseline brain imaging, we report a higher than expected rate of brain progression, in patients without known brain involvement (17.9%), as well as in patients with known pre-treated brain disease. The survival in patients presenting with new brain disease during TDM1 was particularly poor in our study. Interestingly, 4/7 (57.1%) of these patients had associated extra-cranial progression. All but one patient received brain-directed therapy, which was WBRT in 5, but only one patient was suitable for stereotactic RT (defined in the UK National Health Service since 2013 as calculated disease volume less than 20CC) and median time from diagnosis of CNS disease to death was 5.7 months.

No radiological responses in the brain were reported in our study, possibly a reflection of prior brain treatment in all 16 patients, only one of whom had progressing disease at commencement of T-DM1. In contrast, a study of patients with untreated (n=2) or progressing (n=8) brain metastases, reported three partial responses to T-DM1, including one in an untreated brain, with a median intra-cranial PFS of 5 months [7]. A recently published case series of 39 patients with brain metastases treated with T-DM1 reported a median time to brain progression of 8.6 months, with progression in the brain occurring as the first site of progression in 19 patients (48.7%), of whom only 3 had concurrent extra-cranial progression [8]. Similar to our study population, these patients had received a median of 2 prior lines of chemotherapy for advanced breast cancer, but in contrast, all patients had progressive brain disease when they commenced T-DM1. Despite this, their rate of brain progression on T-



DM1 is similar to the rate (9/16, 56.3%) we report here in the 16 patients with known brain metastases, for whom the median brain-specific PFS was 9.9 months. Taken together, these results suggest that T-DM1 may have contributed to the control of brain disease in the 7/16 patients without brain progression in our trial, as their outcome was similar to patients with untreated brain disease in the French series. CNS penetration by T-DM1 is presumed to result from disruption of the blood brain barrier by the disease and/or its treatment.

The retrospective analysis of the EMILIA trial [4] is the largest available series of brain events in patients treated with T-DM1, reporting brain progression in 16% of patients with known brain disease and 2% of those with no brain disease on baseline imaging. The lack of baseline brain imaging in standard practice is an important difference between our population and that in the EMILIA trial, and may explain the higher rate of new brain disease diagnosed during treatment. All patients in our study population had required previous local therapy to the brain due to symptomatic presentation, potentially reflecting a higher burden of brain disease in our population. Ours was also a more heavily pre-treated group, closer to the TH3RESA trial population [2], and the median OS of 17.8 months in our study is comparable to the 22.7 months in TH3RESA,[9] but not to the 30.9 months in EMILIA. This may also explain the higher rate of brain progression in patients without known brain disease in our study compared to EMILIA.

Arguably, the poor survival in patients developing symptomatic brain disease during T-DM1 therapy requires intervention. One approach would be consideration of prophylactic cranial irradiation (PCI), a strategy employed in extensive stage small cell lung cancer, which prolongs median overall survival in this poor prognosis disease [10]. However, with the prolonged survival now expected for HER2 positive advanced breast cancer patients [11], and brain metastases being a common but not inevitable complication of this disease, it seems inappropriate to expose all patients receiving T-DM1 to the morbidity from PCI. Co-treatment with a HER2-directed TKI would be an alternative strategy: The anti-HER2 TKI lapatinib has central nervous system activity,

with a 6% brain response rate with monotherapy and 20% response rate with capecitabine reported in a phase II trial [12]. Combination of lapatinib with T-DM1 and nab-paclitaxel in HER2-positive advanced breast cancer (including patients with brain metastases) is currently being investigated in a phase I/II trial (NCT02073916). Modest brain activity has also been reported for the pan-HER TKI, neratinib, with an 8% response rate in a small (n=40) phase II study [13], leading to ongoing trials of this agent in combination with chemotherapy. Combination of neratinib with T-DM1 is also under investigation, although patients with symptomatic brain metastases are unfortunately excluded from this phase I/II trial (NCT02236000). A selective anti-HER2 TKI, tucatinib (ONT-380), showed promising CNS activity in combination with T-DM1 in a phase Ib study which has been presented, but not yet published: The authors reported brain responses in 4 of the 12 patients with measurable brain disease and a further 5 patients had disease stabilisation from the combination, which appeared well-tolerated [14].

A more conservative approach would be routine brain imaging in asymptomatic patients starting T-DM1, contrary to current ASCO guidelines for HER2 positive breast cancer[15]. This could allow early intervention with stereotactic brain RT, potentially avoiding the unnecessary cognitive morbidity of WBRT, or systemic toxicity from a TKI. A randomised study investigated the neurocognitive impact of WBRT added to stereotactic RT in patients with 1-3 brain metastases (8.5% breast cancer) and reported better quality of life in patients randomised to stereotactic RT alone, although the time to intracranial failure was shorter than in patients who additionally received WBRT [16]. This may also be the case for patients with multiple metastases, although randomised data are lacking; a large observational study of stereotactic brain RT, for patients (10% breast cancer) with up to 10 brain metastases, reported similar outcomes to patients with 1-3 metastases, suggesting that avoiding the morbidity from WBRT is an alternative, even when brain disease is multifocal [17]. Median survivals of 20-26 months for patients with HER2 positive breast cancer brain metastases selected for stereotactic radiosurgery has been reported in several studies [18-20], therefore this is also an effective treatment for this patient subgroup.

CNS haemorrhage has been previously reported in patients with previously irradiated brain metastases receiving T-DM1 despite (near) normal platelet counts,[21] and may be due to enhancement of radiation necrosis. Importantly, such cases may be amendable to neurosurgical resection[22]. On pathological examination, telangiectasia have been observed; a finding previously reported at extra-cranial sites in patients receiving T-DM1[23, 24]. One of the three cases we report was in a previously irradiated lesion and was successfully treated surgically. Two cases occurred in association with new brain metastases, one patient was anti-coagulated with warfarin and had chronic grade 1 thrombocytopenia due to T-DM1, the second developed grade 2 thrombocytopenia immediately before the haemorrhage, but an association with T-DM1-related telangiectasia cannot be excluded as no neurosurgical intervention was attempted for either case.

## **Conclusions**

In our study, the development of new brain disease on T-DM1 was more common than previously reported, and survival from diagnosis with symptomatic progression was poor. Larger, prospective studies are required to determine whether baseline brain imaging prior to commencing T-DM1 is indicated to identify asymptomatic brain disease that can be treated with stereotactic radiotherapy, or surgery. Residual disease may be treated effectively by T-DM1, potentially allowing avoidance or at least deferral of whole brain radiotherapy and its complications.

**Table 1 Baseline characteristics**

	<b>Patients (%) N=55</b>
Gender: Female	55 (100%)
Median age (range)	57.0 years (26-82)
Histological subtype: -Ductal -Lobular -Unknown	45 (81.8%) 3 (5.5%) 7 (12.7%)
Receptor Status -Hormone receptor positive -Hormone receptor negative	35 (63.6%) 20 (36.4%)
Median number of lines of treatment for advanced breast cancer (range)	2 (0-6)
Prior lapatinib	27 (49.1%)
Prior pertuzumab	8 (14.5%)
Sites of metastatic disease: -Bone -Visceral -Brain	36 (65.5%) 44 (80.0%) 16 (29.0%)
Type of brain disease -Parenchymal -leptomeningeal (LM) -mixed -none	15 (27.3%) 0 1 (1.8%) 39 (70.9%)
Prior treatment to brain disease: -Stereotactic RT -Whole brain RT -Stereotactic + whole brain RT -Surgery and stereotactic RT	4/16 (25.0%) 9/16 (56.3%) 1/16 (6.3%) 2/16 (12.5%)

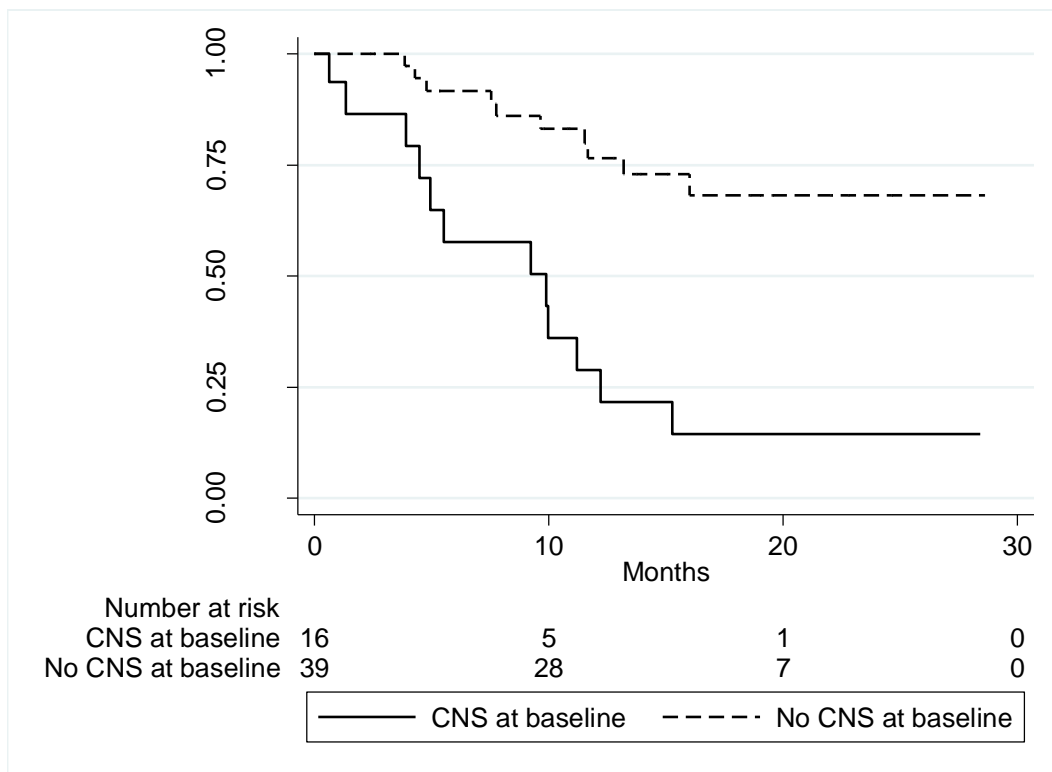
RT=Radiotherapy

**Table 2 Brain disease, treatment and outcomes**

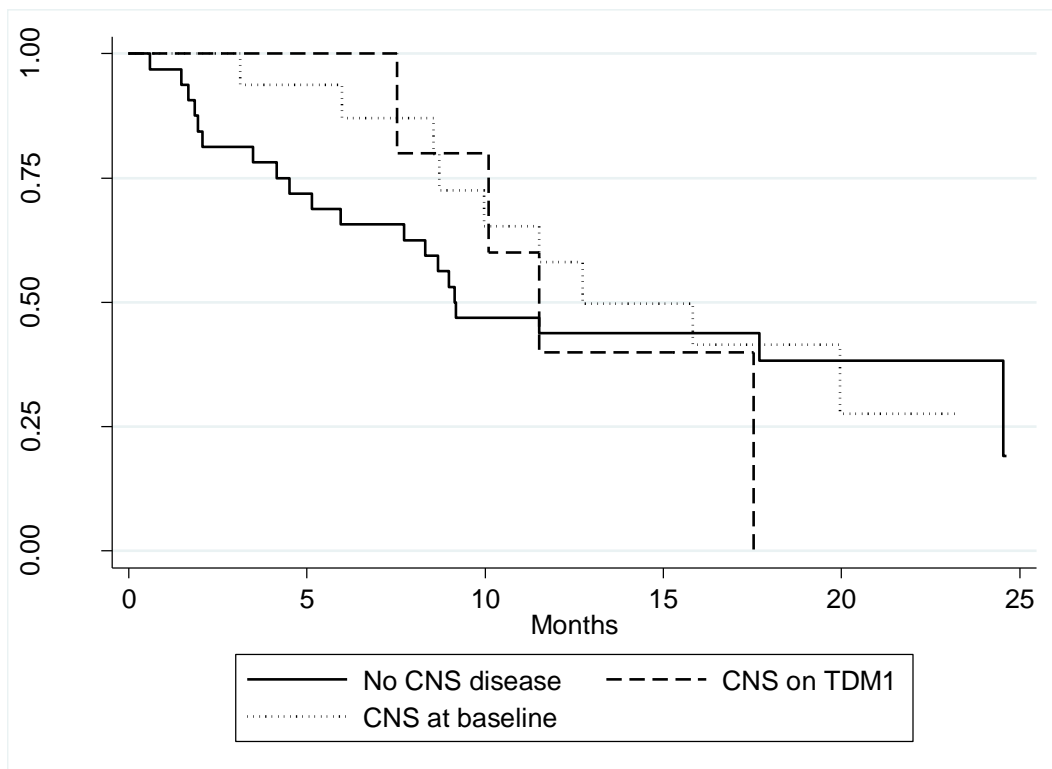
	<b>Patients with baseline brain metastases N=16</b>	<b>Patients with development of LMD and/or brain metastases during T-DM1 N=7</b>
Type of brain disease on progression: -parenchymal only -Leptomeningeal only -No progression	5 (31.3%) 4 (25.0%) 7 (43.8%)	5 (71.4%) 2 (28.6%) -
Treatment of brain progression during T-DM1: -Local therapy -Whole brain RT -Stereotactic RT -None -Systemic therapy -No progression	5 (50%) 2 (12.5%) 3 (18.8%) 3 (18.8%) 1 (6.3%) 7 (43.4%)	6 (85.7%) -5 (71.4%) -1 (14.3%) 1 (14.3%) 0 Not applicable
Median time to CNS progression (95% CI)	9.9 months (3.9-12.2)	7.5 months (3.8-9.6)
Median OS (95% CI)	15.3 months (4.7-not reached)	12.4 months (10.5-17.8)

RT=radiotherapy

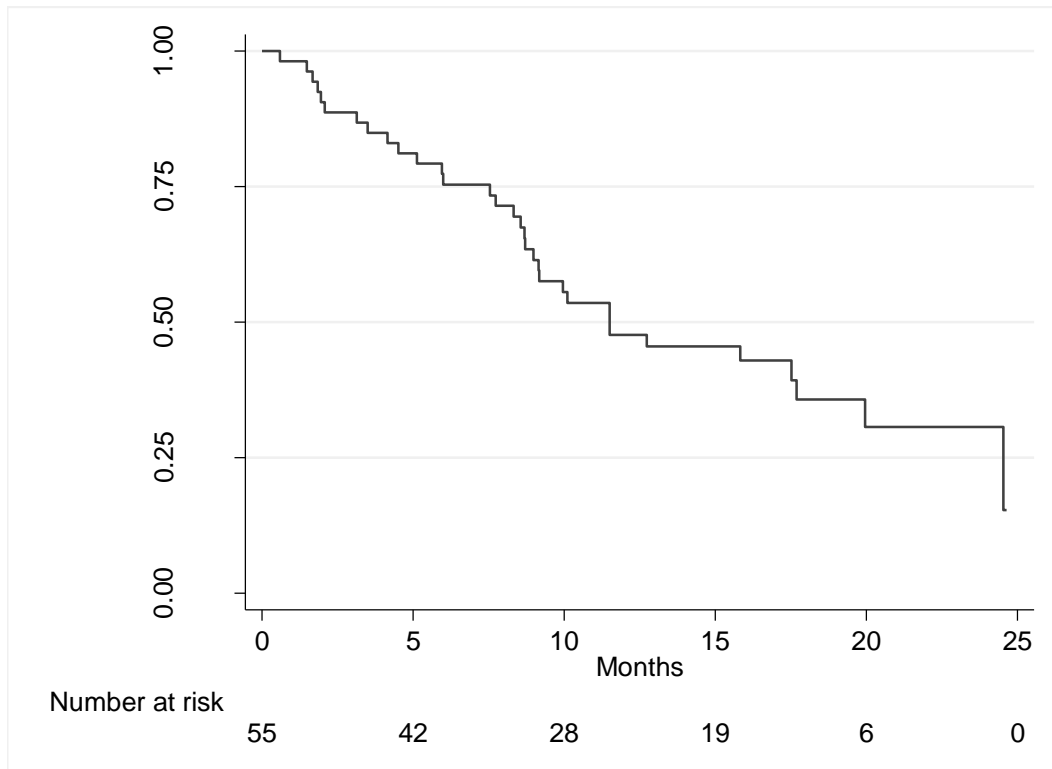
**Figure 1A Time to brain progression in all patients by baseline CNS disease status**



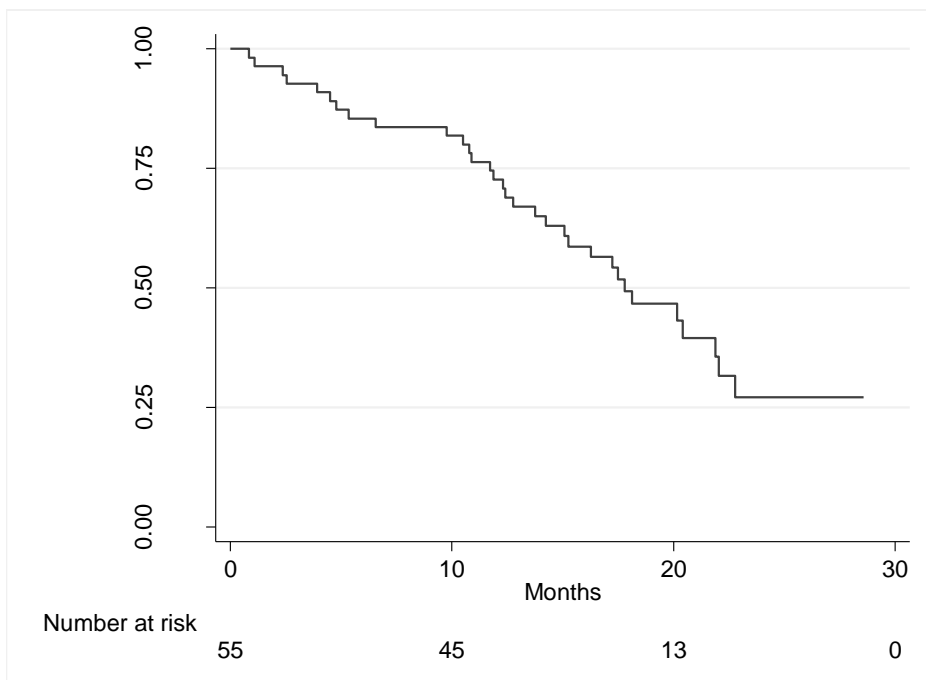
**Figure 1B Time to extracranial disease progression in all patients by baseline CNS status**



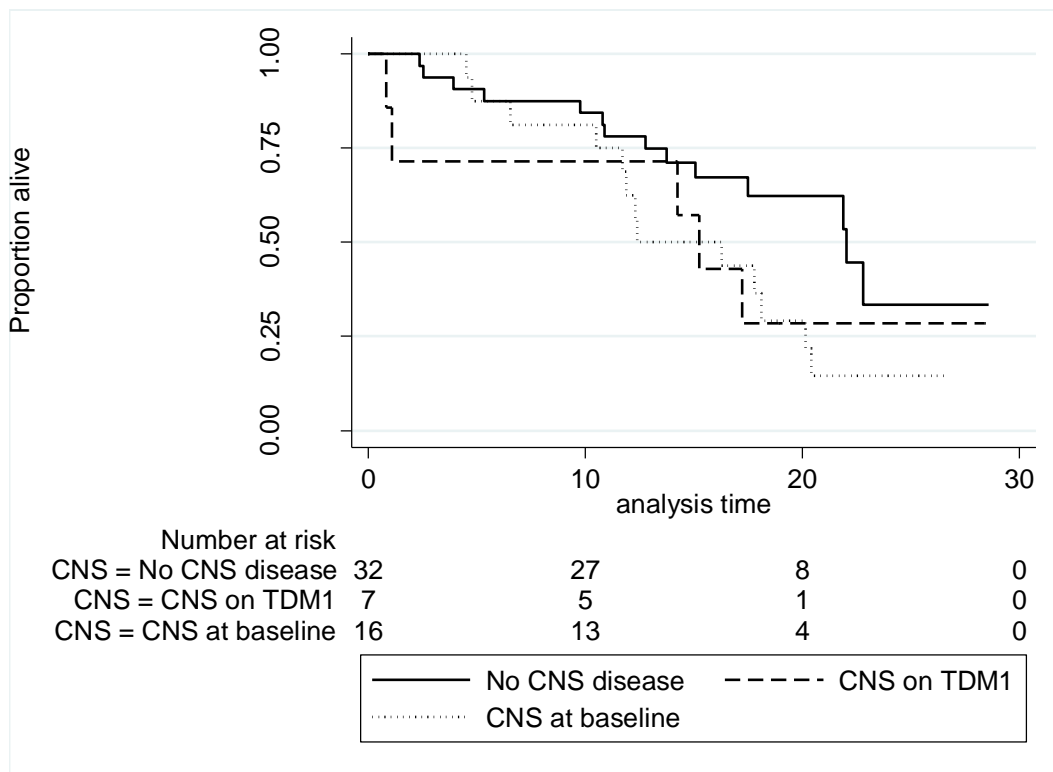
**Figure 2A. Time to extra-cranial disease progression in all patients**



**Figure 2B: Overall survival in all patients**



**Figure 3: Median Survival in patients by CNS status:**







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