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Safety and efficacy of T-DM1 in patients with advanced HER2-positive breast cancer The Royal Marsden experience

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ABSTRACT

Background: Ado-trastuzumab emtansine (T-DM1) is standard of care for patients with advanced HER2+ breast cancer who relapse within 6 months of adjuvant trastuzumab or progress on first-line anti-HER2 therapy. We evaluated its safety and efficacy in our real-world population.

Methods: We identified patients on T-DM1 from 01/01/2014 to 12/03/2018 from our electronic records. Patients', tumour characteristics, safety and efficacy outcomes were recorded. Chi-squared/Fishers exact test and Kaplan-Meier methods were utilised.

Results: 128 patients receiving T-DM1 were included in the analysis with a median age of 55 years (26–85). 89.8% of patients had ECOG PS 0-1 and 21.1% had presented with *de novo* metastatic disease. 57.8% had ER-positive disease and 38.3% central nervous system involvement. 88.3% of patients had received trastuzumab for advanced disease (with pertuzumab in 28.9%) and 11.7% had only received trastuzumab in the adjuvant setting.

Grade ≥3 adverse events occurred in 35.9% of patients. These were liver toxicity (19.5%), anaemia (6.2%) and thrombocytopenia (4.7%). Peripheral neuropathy of any grade was reported in 21.9% of cases, bleeding in 9.4% and ejection fraction decline in 5 patients.

Median progression-free survival was 8.7 months and overall survival 20.4 months. Prior pertuzumab did not influence survival outcomes.

Conclusions: The safety of T-DM1 in our population is similar to available literature, although we observed higher rates of peripheral neuropathy and deranged liver function. These findings are relevant for the potential role of TDM-1 in the curative setting.

Introduction

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a microtubule inhibitor, DM1 [1]. Based on the results of the EMILIA and TH3RESA studies [2–5], T-DM1 has become the standard therapeutic option for advanced breast cancer in case of recurrence on or within six months after completion of adjuvant treatments targeting the human epidermal growth factor receptor 2 (HER2) or in the second-line setting upon disease progression on first-line targeted agents [6,7].

The EMILIA study documented a median progression-free survival (PFS) of 9.6 months and median overall survival (OS) 30.9 months, superior to the comparator arm of capecitabine and lapatinib [2,5]. The TH3RESA trial demonstrated median PFS of 6.2 months and OS of 22.7 months in patients receiving TDM-1 following at least two prior anti-HER2 therapies for advanced breast cancer [3,4]. These findings suggest that some patients derived prolonged benefit from T-DM1. These studies also reported increased rates of any grade transaminitis in 22.4% and any grade thrombocytopenia in 28.0% of patients (which were grade 3 in 4.3% and 12.9% respectively). Such toxicities may be challenging to manage in an increasingly pre-treated cohort of patients with reduced bone marrow reserve and in the context of liver metastatic involvement and therefore require careful monitoring. Data on outcomes of T-DM1 in the real world are derived from small experiences mainly focusing on efficacy [8–10], whereas there are limited data on safety, especially in the long-term.

Therefore, we sought to evaluate the safety and efficacy of T-DM1 in a population of real-world patients who received it in our Institution following regulatory approval, with particular attention to chronic liver and haematological toxicity.

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Materials and methods

We retrospectively identified and reviewed the electronic medical records of 134 patients treated with T-DM1 at The Royal Marsden NHS Foundation Trust from 01/01/2014 to 12/03/2018 from our records. This time window was chosen since T-DM1 became available in the United Kingdom in 2014 and to ensure adequate follow-up. Patients' characteristics (including, age, Eastern Cooperative Oncology Group [ECOG] performance status [PS], date and cause of death, BRCA mutational status) and tumour characteristics (including stage at diagnosis, oestrogen receptor (ER), progesterone receptor (PgR) and HER2 status and sites of metastatic involvement) were extracted from our electronic medical records, along with early and advanced stage treatment history and outcomes (including dosing, schedule, responses, duration, adverse events and their grading and reason for discontinuation).

HER2 positivity was defined as a score of 3 on immunohistochemistry or single-probe average HER2 copy number ≥ 4.0 signals/cell or dual-probe HER2/CEP17 ratio ≥ 2.0 with an average HER2 copy number < 4.0 signals/cell on in situ hybridization according to the current international guidelines [11].

We defined advanced HER2-positive breast cancer as patients who had relapsed with radiological features of metastatic disease following a previous diagnosis of early stage HER2 positive disease, or presented with *de novo* stage IV disease. If a metastatic biopsy had been performed, we excluded patients with disease which was not confirmed as HER2-positive on their most recent metastatic biopsy. We also excluded patients who had not been treated with palliative intent (such as those with disease potentially amenable to radical therapy) and those who received treatment in other institutions. To be eligible for this analysis, patients had to have received T-DM1 in the advanced setting.

According to the Food and Drug Administration definitions [12], overall response rate (ORR) was calculated as the proportion of patients achieving partial response (PR) or complete response (CR) on systemic therapy according to a definition of treatment failure based on clinical, radiological and biochemical findings at different time intervals. Clinical benefit rate (CBR) was calculated as the proportion of patients achieving stable disease (SD), partial response (PR) or complete response (CR) on systemic therapy. Adverse events were calculated based on the proportion of patients experiencing a side effect following treatment initiation; adverse events were rated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [13]. PFS was defined as time from commencement of any line of systemic therapy until disease progression or death. Non-responding patients were counted as PFS event on the response assessment date. Progression-free patients were censored at the last follow-up date. OS was calculated as time from commencement of first-line systemic therapy until death from any cause. Surviving patients were censored at the last follow-up date. This analysis was approved as a service evaluation by The Royal Marsden NHS Foundation Trust/The Institute of Cancer Research Committee for Clinical Research.

Descriptive analysis method was used to summarise the data using counts and percentages for categorical variables and for the continuous non-normal variables using median and range or interquartile range. Proportion of patients responding at each re-imaging was calculated with 95% confidence interval. Chi-squared and Fishers exact test used as appropriate to compare the response rates in the patient groups. Kaplan Meier method was utilised for the calculation of OS time from date of treatment initiation to death or last follow-up date. Kaplan Meier method was also used for the calculation of PFS time from the start of treatment initiation to disease progression or death; progression-free and lost to follow-up patients were censored at last follow-up date. Median time to event reported with 95% confidence interval and compare patient groups using Log-rank test.

Table 1
Demographics, disease characteristics and previous anti-HER2 therapies at treatment initiation (N = 128) [ECOG PS: performance status; ER: oestrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; CNS: central nervous system]

Age (years)	Median (range)	55 (26–85)	
	Mean	55.6	
Charlson Comorbidity Index	Median (range)	1 (0–7)	
	Mean	1.35	
Variables	N	%	
Menopausal status	Premenopausal	20	15.6
	Perimenopausal	13	10.2
	Postmenopausal	95	74.2
BRCA status	Negative	14	10.9
	Unknown	114	89.1
De novo metastatic presentation	27	21.1	
ECOG PS	0	35	27.3
	1	80	62.5
	2	10	7.8
	3	3	2.4
ER status	Negative	54	42.2
	Positive	74	57.8
PgR status	Negative	72	56.3
	Positive	51	39.8
	Unknown	5	3.9
HER2 status	Positive	128	100.0
Bony metastases	82	64.1	
Liver metastases	71	55.5	
Lung metastases	62	48.4	
Nodal metastases	78	60.9	
CNS metastases	49	38.3	
Chest wall involvement	26	20.3	
Line of therapy	First line (early relapse)	15	11.7
	Second and subsequent lines	113	88.3
Prior trastuzumab	Curative	63	49.2
	Palliative	113	88.3
	Total	128	100.0
Prior pertuzumab	Curative	2	1.6
	Palliative	37	28.9
	Total	39	30.5

Results

Of 134 patients diagnosed receiving T-DM1 and assessed for eligibility, 128 patients were included in the analysis. Six patients were excluded as they received T-DM1 within a clinical trial in the curative setting. The median age of eligible patients at treatment initiation was 55 years old (range 26–85). Patients had a median Charlson Comorbidity Index of 1 (range 0–7).

As shown in Table 1, at treatment initiation 115 patients (89.8%) of patients had ECOG PS 0-1. Disease presentation was *de novo* metastatic in 27 patients (21.1%). ER status was positive in 74 patients (57.8%). Metastatic disease involved the bones in 82 patients (35.9%), the liver in 71 (55.5%), the lungs in 62 (48.4%), the lymph nodes in 78 (60.9%) and the chest wall in 26 (20.3%). Forty-nine patients had central nervous system (CNS) secondary involvement (38.3%) and in 4 this was the only site of metastatic spread. The median number of T-DM1 cycles given was 11 (range 1–67). The majority of patients received T-DM1 after prior palliative anti-HER2 treatment, which was trastuzumab in 113 (88.3%) and pertuzumab in 37 (28.9%). Only 15 patients (11.7%) received T-DM1 in the first-line setting following early disease relapse after completion of curative anti-HER2 treatment.

Out of the 49 patients with CNS disease, 30 (61.2%) had ER-positive breast cancer and 13 (26.5%) had a previous *de novo* metastatic presentation. Four of these patients had early recurrence and had received trastuzumab only in the curative setting and 45 had received previous anti-HER2 treatment for advanced disease. All had received prior stereotactic or whole brain radiotherapy.

Table 2 outlines the safety profile of T-DM1 in our population of patients. Grade ≥ 3 adverse events occurred in 46 patients (35.9%)

Table 2
Adverse events observed in the overall cohort until April 2019 (N = 128).

Adverse events		N	%
Neutropenia (any grade)		29	22.7
Worst grade of neutropenia	1	21	16.4
	2	7	5.5
	3	1	0.8
Febrile neutropenia		0	0.0
Anaemia (any grade)		51	39.2
Worst grade of anaemia	1	29	22.6
	2	14	10.9
	3	8	6.2
Thrombocytopenia (any grade)		56	43.8
Worst grade of thrombocytopenia	1	32	25.0
	2	9	7.0
	3	5	3.9
	4	1	0.8
Oral mucositis		4	3.1
Worst grade of oral mucositis	1	2	1.6
	2	1	0.8
	3	1	0.8
Diarrhoea		7	5.5
Worst grade of oral diarrhoea	1	3	2.3
	2	1	0.8
	3	3	2.3
Nausea		33	25.8
Worst grade of nausea	1	20	15.6
	2	12	9.4
	3	1	0.8
Fatigue		82	64.1
Worst grade of fatigue	1	46	35.9
	2	33	25.8
	3	3	2.3
Skin rash		10	7.8
Worst grade of skin rash	1	6	4.7
	2	4	3.1
Spider naevi		5	3.9
Deranged liver function		88	68.8
Worst grade of deranged liver function	1	41	32.0
	2	22	17.2
	3	24	18.7
	4	1	0.8
Peripheral neuropathy		28	21.9
Worst grade of peripheral neuropathy	1	13	10.1
	2	12	9.4
	3	3	2.3
Cardiac toxicity		5	3.9
Pulmonary toxicity		1	0.8
Infections requiring antibiotics		44	34.4
Bleeding		12	9.4
Dose delays		55	43.0
Dose reductions		46	35.9
Lowest dose given	3.6 mg/Kg	82	64.1
	3.0 mg/Kg	29	22.7
	2.4 mg/Kg	17	13.3
Reason for dose reduction	Anaemia	2	1.6
	Thrombocytopenia	8	6.2
	Deranged liver function	8	6.2
	Fatigue	11	8.6
	Peripheral neuropathy	14	10.9
	Nausea	1	0.8
	Skin toxicity	1	0.8
	Other	1	0.8
Treatment discontinuation		111	86.7
Reason for discontinuation	Anemia	2	1.6
	Thrombocytopenia	4	3.1
	Deranged liver function	2	1.6
	Fatigue	4	3.1
	Mucositis	1	0.8
	Peripheral neuropathy	1	0.8
	Disease progression	94	73.4
	Other	3	2.3

(95% confidence interval [CI] 27.6–44.9%). These involved more frequently liver toxicity in 25 (19.5%), anaemia in 6.2% (n = 8) and thrombocytopenia in 6 (4.7%). There were no episodes of febrile neutropenia. The number of patients with grades 1, 2 and 3 neuropathy were: 13 (10.1%), 12 (9.4%) and 3 (2%), respectively. Peripheral neuropathy was first reported following a median of 5 cycles of T-DM1 (range 1–46) (Fig. 1). Bleeding was reported in 12 patients (9.4%) and decline in the left ventricular ejection fraction ≥10% and/or below 50% in 5 patients.

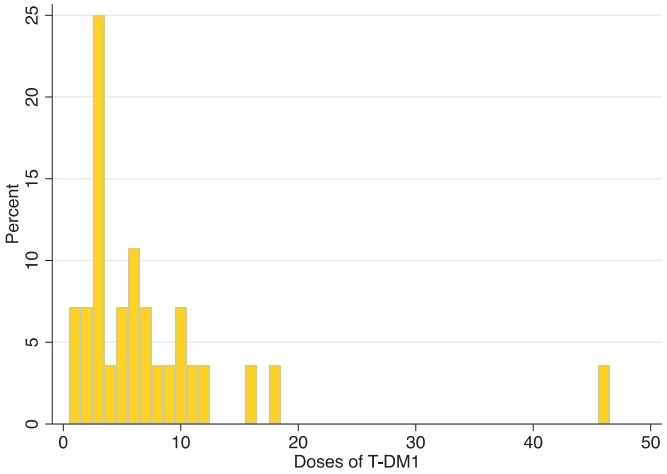

Fig. 1. Time to first onset of neuropathy for the 28 patients who developed neuropathy.

T-DM1 was discontinued due to toxicity in 14 patients (12.8%) (95% CI 7.2–20.6%). Dose delays were required in 58 patients (45.3%) and lasted a median 21 days, with 57 patients (98.3%) warranting deferrals for more than 7 days. Forty-five patients (36.0%) required dose reductions down to 3.0 mg/Kg in 29 (22.7%) and 2.4 mg/Kg in 17 (13.3%). Most common reasons for dose reductions included peripheral neuropathy in 14 cases (30.4%), fatigue in 11 (23.9%), thrombocytopenia in 8 (17.4%) and deranged liver function in 8 (17.4%).

In the overall cohort, ORR was 64.2% and CBR was 82.5% (Table 3). Among the patients with CNS involvement and measurable extra-CNS disease, at first systemic response assessment 9 (19.1%) had stable disease, 29 (61.7%) partial response and 6 (12.8%) disease progression. Among the 46 patients with measurable disease in the CNS, 28 patients (60.9%) had disease response specifically in the brain. In the overall cohort, median PFS was 8.7 months (95% CI 7.0–10.1 months) and did not change significantly based on prior use of trastuzumab and pertuzumab (Table 4). Eighty-seven patients (68.0%) had died at the time of the analysis, due to their breast cancer in 84 cases (96.5%). Median OS was 20.4 months (95% CI 17.0–22.1 months), which was longer for patients who had not received trastuzumab in the curative setting (22.1 months, 95% CI 20.2–35.4 months) compared to those who had received it (16.6, 95% CI 13.7–20.4 months) (p *0.025*), but no differences were observed based on prior use of pertuzumab. The Kaplan-Meier curves for median PFS and OS are shown in Fig. 2.

Table 3
Best responses in patients who underwent a radiological response assessment (N = 120). [ORR: overall response rate; CBR: clinical benefit rate; PD: disease progression; SD: stable disease; PR: partial response; CR: complete response]

Parameter		*N*	%
Best response	PD	21	17.5
	SD	22	18.3
	PR	67	55.8
	CR	10	8.3
ORR	77	64.1	
CBR	99	82.4	

Table 4
Survival outcomes in patients eligible for the analysis ($N = 126$). [ORR: overall response rate; CBR: clinical benefit rate; PD: disease progression; SD: stable disease; PR: partial response; CR: complete response; PFS: progression-free survival; OS: overall survival; CI: confidence intervals; NR: not reached]

Parameter			N	Months	95% CI	*p* value
Median PFS	Overall	128	8.7	7.0–10.1	–	
	Prior curative trastuzumab*	No	64	9.2	7.7–11.5	0.582
		Yes	62	7.4	5.3–10.1	
	Prior palliative trastuzumab	No	14	5.3	1.3–15.8	0.138
		Yes	112	8.7	7.5–10.1	
	Prior curative pertuzumab*	No	124	8.6	7.0–10.1	0.658
		Yes	2	6.4	6.4-NR	
	Prior palliative pertuzumab	No	89	8.3	6.1–10.1	0.610
		Yes	37	8.7	6.6–11.3	
Median OS	Overall	128	20.4	17.0–22.1	–	
	Prior curative trastuzumab*	No	64	22.1	20.2–35.4	0.025
		Yes	62	16.6	13.7–20.4	
	Prior palliative trastuzumab	No	14	17.0	2.5–43.0	0.367
		Yes	112	21.1	16.6–22.9	
	Prior curative pertuzumab*	No	124	20.4	16.6–22.1	0.580
		Yes	2	17.0	17.0-NR	
	Prior palliative pertuzumab	No	89	20.6	17.5–22.9	0.859
		Yes	37	18.5	13.2–37.4	

* Regardless of subsequent systemic treatments given in the palliative setting.

Discussion

The treatment paradigm of advanced HER2-positive breast cancer in later lines of therapy is substantially evolving. Recently, the HER2CLIMB study has documented a PFS and OS benefit for patients receiving the tyrosine kinase inhibitor tucatinib in combination with capecitabine and trastuzumab following progression on T-DM1 in a challenging population, including almost half patients with brain metastatic involvement [14]. The recent DESTINY-Breast01 study has also confirmed durable responses with the antibody-drug conjugate trastuzumab deruxtecan in patients who had previously received T-DM1 [15]. Therefore, the availability of novel and effective targeted treatment options in later lines of therapy makes it even more important to carefully evaluate the safety profile of T-DM1 in less selected populations. Furthermore, the KATHERINE study has confirmed the benefit of 14 cycles of T-DM1 for patients with residual disease following neoadjuvant systemic therapy [16]; the potential emergence of TDM-1 into the curative setting emphasises the importance of evaluating real world toxicity.

The rates of grade ≥ 3 adverse events in our cohort were similar to published data although we observed a higher incidence of any grade peripheral neuropathy (21.9%) and thrombocytopenia (43.8%) and grade ≥ 3 deranged liver function (19.5%), likely because the majority of these patients had received previous taxane-based chemotherapy and more than half had liver metastatic involvement. The occurrence of spider naevi has previously been reported in patients on long-term T-DM1 [17]: in our cohort, 5 patients developed spider naevi on T-DM1

We found a favourable ORR (64.1%) and a median PFS similar in our series (8.7 months) to the published data (EMILIA: 9.6 months; TH3RESA: 6.2 months) which is consistent with the fact that our analysis included a significant proportion of patients who had previously received trastuzumab. Interestingly, 60.9% of patients with measurable disease in the brain had disease response in the CNS. Nonetheless, this cannot be attributed exclusively to T-DM1 as these patients have also received stereotactic and/or whole brain radiotherapy to that site, which might explain our better CNS disease response rates compared to those reported in literature [18]. OS outcomes were inferior in our patients (20.4 months) compared to trial findings (EMILIA: 29.9 months; TH3RESA: 22.7 months) as would be expected in a less selected population. Moreover, central nervous system metastatic involvement was present at baseline in a higher proportion of patients (38.3%) included in our analysis compared with the registration studies and this may account for the less favourable OS outcomes. Nonetheless, our study included almost one third of patients who had received prior pertuzumab (in any setting) which suggests that T-DM1 remains a valuable systemic treatment option also in the context of current standard-of-care approaches involving dual anti-HER2 blockade.

This analysis has some limitations. First, it is retrospective which implies that patient heterogeneity and differences in timing and methods of response evaluation could have introduced bias in the response and PFS analysis. Our population is also mono-institutional, and findings would need to be confirmed in larger, multicentre observational cohorts.

Nonetheless, this remains the largest cohort of patients receiving T-DM1 for advanced HER2-positive breast cancer focusing not only on its efficacy but also on its safety profile, which represents an increasingly relevant aspect in the context of the evolving therapeutic paradigm for this disease subtype. Our findings confirm that T-DM1 is a valuable systemic treatment option for real-world patients whose breast cancer is progressing on dual anti-HER2 blockade.

Funding source

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Ethical approval

This research project has been reviewed and approved as a Service Evaluation by The Committee for Clinical Research at The Royal Marsden NHS Foundation Trust/Institute for Cancer Research.

Declaration of Competing Interest

Dr Battisti has received travel grants from Pfizer and Genomic Health and speaker fees from Pfizer. Dr Ring has received honoraria for ad hoc advisory boards and for ad hoc presentations from Lilly, Pfizer, Novartis, Roche and MSD. The other authors have no conflict of interest to declare.

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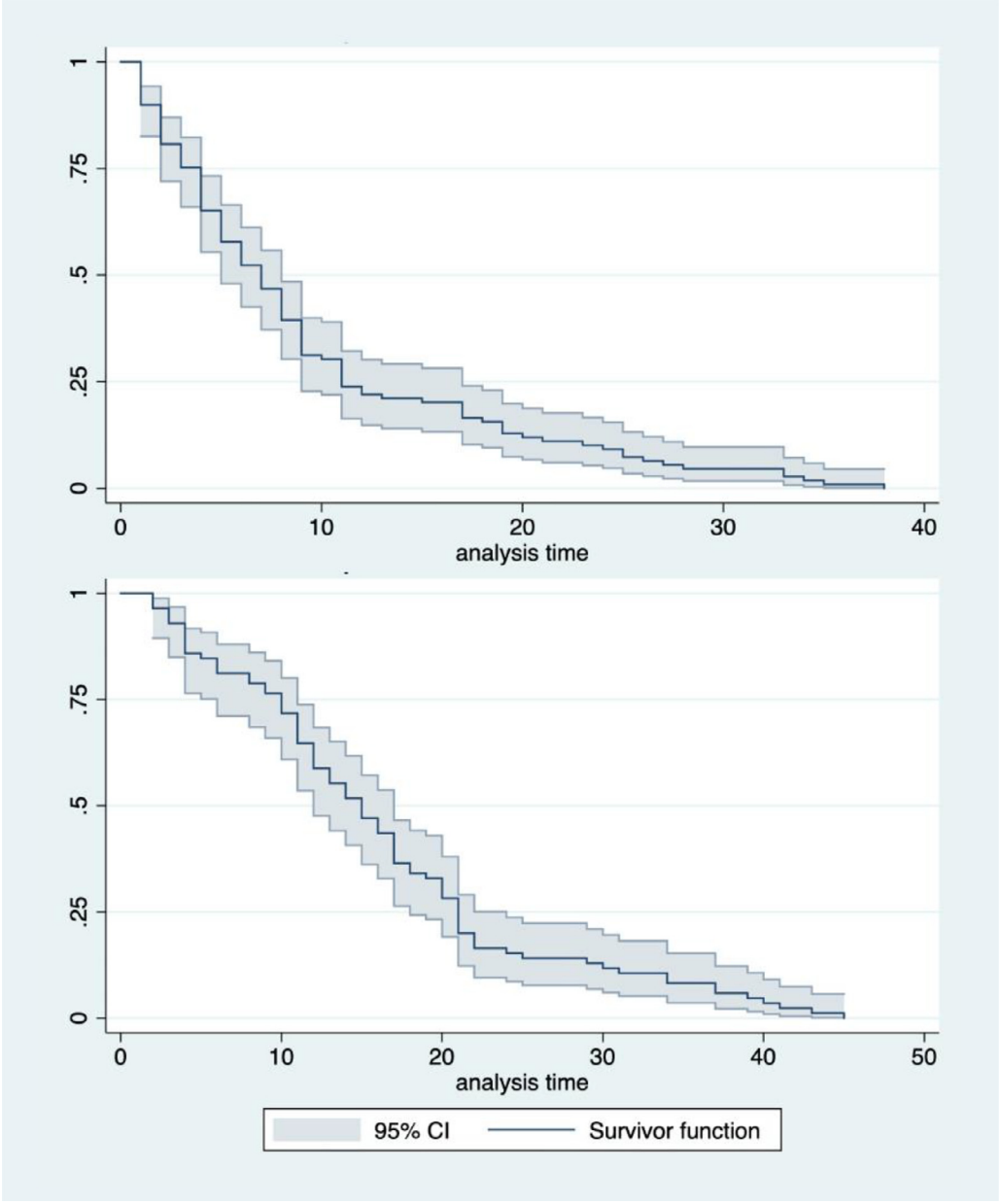

Fig. 2. Kaplan Meier for median progression-free survival (top) and overall survival (bottom) in the overall cohort.

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