Retrospective analysis of HER2 therapy interruption in patients responding to the treatment in metastatic *HER2+* breast cancer

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ABSTRACT

Introduction Human epidermal growth factor receptor 2 (HER2)-targeted-therapy regimens can lead to prolonged tumour responses in metastatic *HER2+* breast cancer. Clinical trials have concerned use of HER2-targeted agents until disease progression, but it is unknown whether the therapy can be interrupted in cases of a good response.

Methods Single institute, retrospective collection of data on patients with *HER2+* metastatic breast cancer (n=68) was carried out through a pharmacy search for patients who had received trastuzumab in 2006–2014. Clinical and pathological factors, treatment history and survival data were collected from patient records.

Results Median survival in metastatic disease (all patients) was 32 months and survival times were dramatically different in patients with and without trastuzumab as adjuvant or primary metastatic disease (median 16, 77 and 35 months, respectively; p=0.0004). More importantly, HER2 therapy was intentionally interrupted in 21 responding patients, and these patients experienced long HER2-therapy-free intervals (median 51 months), with excellent long-term survival. A lack of previous adjuvant trastuzumab was the only statistically significant factor predictive of HER2 therapy interruption.

Conclusions These results from our retrospective study show that HER2 therapy interruption in patients with metastatic *HER2+* breast cancer, who have responded to the therapy, is associated with low risk of rapid disease progression. Study suggests that therapy interruption in cases of response and reinitiation in progression is feasible.

Key questions

What is already known about this subject?

► Clinical trials have investigated use of human epidermal growth factor receptor 2 (HER2) antibodies, such as trastuzumab, in metastatic disease until severe side effects or disease progression.
► Some case reports have described that patients whose trastuzumab treatment is discontinued in response can remain disease progression free for long periods of time.
► Experts agree that optimal duration of HER2 therapy is unknown in complete responders.

What does this study add?

► Current study presents the largest patient cohort with metastatic *HER2+* breast cancer whose HER2 therapy was interrupted in response.
► HER2 therapy interruption in response is associated with low likelihood of rapid disease progression.
► Long-term outcomes are excellent for the patients whose HER2 therapy was interrupted in response.

How might this impact on clinical practice?

► HER2 antibody interruption in responding patients with metastatic *HER2+* is feasible.
► Prospective studies on the therapy interruption in response are warranted.

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INTRODUCTION

The human epidermal growth factor receptor 2 gene (*HER2*) is amplified in ~20% of breast cancers. It was earlier associated with an increased relapse rate in localised disease and shorter overall survival in metastatic disease.[1 2] HER2-targeted therapeutic agents, such as trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1) and lapatinib, have changed disease outcomes in this subset of breast cancer.[3–6] Treatment with trastuzumab as an adjuvant can decrease the relative risk of relapse by 46%–52% at 2–3.5 years,[7 8] and trastuzumab and trastuzumab+pertuzumab

chemotherapy combinations have been shown to lead to impressive overall survival in metastatic disease.[3 4 9]

Treatment guidelines concerning metastatic *HER2+* breast cancer suggest that HER2-targeted agents should be included in treatment regimens of multiple lines of therapy, since this has been linked to improved patient outcomes.[5 6 10] Trastuzumab treatment has been linked to long-term survival, especially in patients who have remained progression free for more than 2 years under the treatment.[11] Clinical studies on HER2-targeted agents have been concerned with HER2 therapy until disease progression, but there is a lack of evidence regarding treatment

discontinuation in cases of response. Some small case report series have characterised patients with *HER2+* breast cancer who have achieved complete responses with chemotherapy and trastuzumab-containing regimes, and patients have remained disease free without HER2 therapy for years.[12 13] HER2 therapies are costly and prolonged treatment leads to marked drug-related costs. Recent evidence with immune-activating cancer drugs, such as PD-1 and CTLA-4 inhibitors, can result in long disease progression-free periods even after short exposures to these agents.[14] Since mode of action of trastuzumab is related both to signal inhibition and immunoactivation,[15 16] it is possible that same phenomenon would also be seen with *HER2+* breast cancers treated with trastuzumab.

In our institute, in contrast to clinical trial protocols, we have aimed to discontinue trastuzumab treatment if a patient with metastatic *HER2+* breast cancer has achieved prolonged response for this agent. In the current work, we systematically collected data on all the patients with metastatic *HER2+* breast cancer who were treated with trastuzumab in our institute in 2006–2014. The results showed that in 30% of the patients, trastuzumab treatment was discontinued as a result of a long-lasting response or a response and toxicity. More importantly, most patients experienced a prolonged progression-free interval without treatment with HER2-targeted agents.

PATIENTS AND METHODS
Patient data
All patients who had received at least one dose of intravenous trastuzumab at Oulu University Hospital in 2006–2014 were retrospectively identified from the pharmacy records. From the electronic patient records, we identified those who had received trastuzumab for the treatment of metastatic breast cancer and excluded all those who had received the drug only as adjuvant treatment of breast cancer or as treatment for gastric cancer (figure 1). *HER2* positivity was characterised by the presence of *HER2* amplification in chromogenic in situ hybridisation.

The patient's age, date of diagnosis, date of metastatic disease, TNM staging, histology, tumour grade, Ki-67 staining, oestrogen (OR) and progesterone (PR) status, adjuvant/metastatic treatment regimens and times were collected from the electronic patient records. Survival in cases of metastatic disease was calculated from the time of histological or if not available, radiological identification of metastatic disease to death or end of follow-up. Patients whose HER2 therapy was interrupted were characterised by having a planned HER2 therapy interruption in connection with a response lasting >12 months or with a response plus severe suspected HER2 therapy-related adverse events. HER2 therapy discontinuation length was defined from the date of the last administration of trastuzumab (in the longest HER2 therapy discontinuation period) to
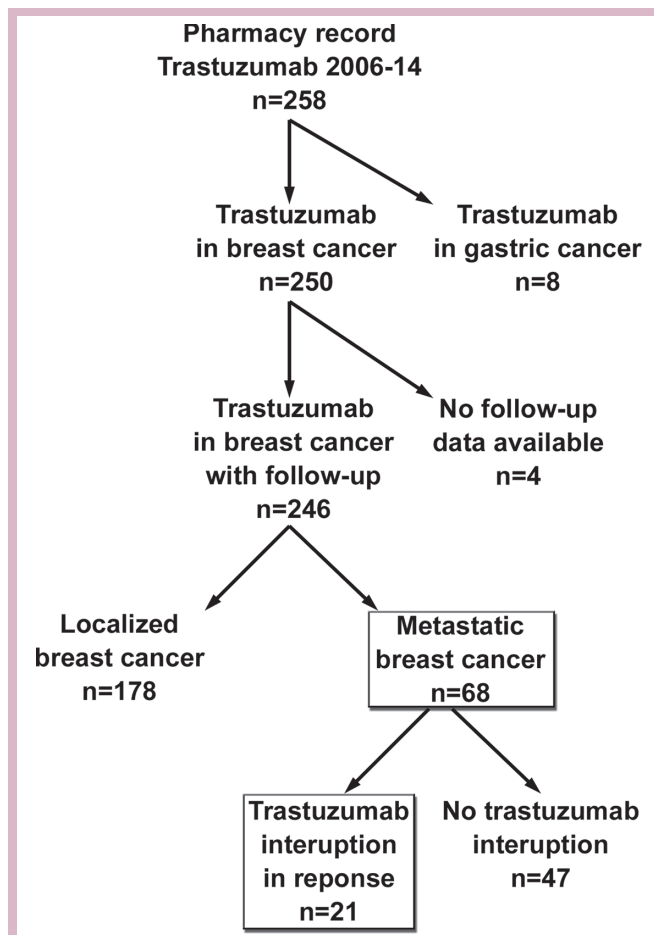

Figure 1 Collection of the patient cohort from pharmacy records.

the date of drug reinitiation, death or end of follow-up (10 November 2016). Response before HER2 therapy interruption was retrospectively analysed from electronic patient records by two independent investigators (JPK, PK), and patients were grouped into complete or near-complete responders or others with 100% concordance.

HER2 therapy discontinuation was carefully weighted for the risks on individual bases and discussed with the patient. In some cases, treatment was discontinued based on patient's preference only. Ethics commitee statement for the clinical practice was not sought since optimal duration of HER2 therapy remains unknown and therapy interruption in prolonged response has been an institutional policy.

Statistics
IBM SPSS Statistics V.22.0 for Windows was applied for statistical analysis. The reported p values are from two-sided χ^2 tests and the Mann-Whitney test. Survival was analysed by using the Kaplan-Meier method with the log-rank test. Probability values below 0.05 were considered significant.

RESULTS

Patient characteristics

We systematically searched the electronic pharmacy records of Oulu University Hospital for all the patients who had received intravenous trastuzumab in 2006–2014. Through the search, we identified 258 patients who had received at least a single dose of the drug. Of these, 68 had received the treatment for metastatic breast cancer and further analysis was limited to this group (figure 1).

The median age at initial diagnosis was 58 years (range 28–83). The median date of initial diagnosis of breast cancer was 24 October 2009 (range 15 January 1992–20 November 2014) and the median date for metastatic disease was 03 May 2010 (range 28 February 2000–20 November 2014). Forty-four (64.7%) patients had localised disease at the time of diagnosis and 25 (36.7%) had received trastuzumab as adjuvant treatment. Of the newer HER2-targeting agents for metastatic disease, 16 (23.5%) patients had received lapatinib, 6 (8.8%) pertuzumab and 2 (2.9%) T-DM1. Primary tumours were commonly T1–2 size or T4. Thirty-eight (55.8%) patients had N1–3 disease while only 10 (18.5%) had N0 disease at the time of diagnosis. Fifty-nine (86.8%) had ductal and 7 (10.3%) lobular histology of the tumour. The tumours were generally aggressive, with 47 (69.1%) patients having grade III tumours and 44 (64.7%) showed high-level Ki-67 staining (>30%). Forty-five (66.2%) and 23 (33.8%) were positive and negative for OR, respectively. Common sites for the first occurrence of metastatic disease were bone only (19; 27.9.5%), multiple sites (20; 29.4%) and visceral only (13; 19.1%) (table 1).

Median survival in metastatic disease (all patients) was 32 months (range 0–200 months; figure 2A). Survival times were dramatically different when the patients were grouped to those who had received trastuzumab as adjuvant treatment, those who had primary metastatic disease or those who had not received trastuzumab as adjuvant treatment, with median overall survival times of 16 months, 35 months, and 77 months, respectively (p=0.00004; figure 2B).

Patients with HER2 therapy interruption

Of the 68 patients with metastatic disease, HER2 therapy was discontinued in 21 (30.9%), i.e. 17 (81%) who had experienced a long-lasting tumour response, and four (19%) with a tumour response and a suspected HER2-therapy-related severe adverse event leading to drug discontinuation. The median age at diagnosis, primary tumour T-stage, N status, histology, Gr, ER positivity, and sites of the first distant metastasis were similar in HER2 therapy-discontinuing and HER2 therapy-continuing patients. In the HER2 therapy discontinuation group, there were more patients who had not received trastuzumab as adjuvant (12 (57%) compared with 7 (14.9%)) in the continuation group), which was the only studied factor reaching statistical significance (p=0.0001) (table 2).

The patients whose HER2 therapy was discontinued had received a median duration of 15 months (range 0–42) of HER2-targeted therapy (trastuzumab or trastuzumab+pertuzumab) before the longest discontinuation period. Most patients had HER2-targeeted therapy in combination with chemotherapy (76.2%) before HER2 therapy interruption, either taxanes (62.5%) or vinorelbine (37.5%). Before HER2 therapy interruption, 38.1% of the patients were complete or near complete responders to the therapy (table 2).

The median duration to HER2 therapy reinitiation or death was 51 months (range 5–124 months) in connection with the longest HER2 therapy discontinuation period (figure 3A). Nine (42.9%) patients had received hormonal therapy during HER2 therapy discontinuation period. There was no difference in HER2 therapy discontinuation length whether patient had received hormonal therapy during HER2 therapy interruption (42 vs 52 months) but the survival inversely affected in the hormonal therapy group (73 months vs not reached, p=0.0077). Furthermore, depth of response did not affect the HER2 therapy discontinuation length but survival in metastatic disease was improved in patients who had complete or near-complete response before discontinuation (not reached vs 73 months, p=0.009). In the HER2 discontinuation group, 10 (47.6%) patients experienced disease progression during the interruption period, leading to HER2 therapy reinitiation. Of the patients whose HER2 therapy was reinitiated, seven (70%) had, at least, long-term disease control (>12 months) during the reinitiated period of HER2 therapy (table 2). Only one (10%) patient experienced rapid disease progression (<6 months) after HER2 therapy discontinuation, and no brain metastasis occurred during the discontinuation period. In six patients, HER2 therapy was discontinued twice and two patients had a third discontinuation period in connection with a deep and prolonged tumour response to a reinitiated HER2 regimen. Median survival in metastatic disease was better in HER2 treatment discontinuation group both in primary metastatic disease (75 vs 24 months, p=0.0001) or in patients without trastuzumab adjuvant treatment (100 vs 41 months, p=0.0001) (figure 3B,C). We were unable to study the effect of HER2 therapy discontinuation to the survival of patients with adjuvant trastuzumab since only one patient had discontinuation event in the subgroup.

DISCUSSION

In the current work, we describe a complete, single-institute retrospective patient cohort with *HER2+* metastatic breast cancer (n=68) who had received at least a single dose of trastuzumab in 2006–2014. Our cohort is limited as regards the number of cases, but the length of follow-up, and inclusion of all patients from a single institute with high follow-up rate makes it valuable. The patient cohort consisted of ~35% of primary metastatic disease cases and ~65% of initial localised disease cases.

Table 1   Demographics of the patients with HER2+

	n (%)
Histology	
Ductal	59 (86.8)
Lobular	7 (10.3)
Unknown	2 (2.9)
Oestrogen receptor status	
Positive	45 (66.2)
Negative	23 (33.8)
Progesterone receptor status	
Positive	27 (39.7)
Negative	41 (60.3)
Ki-67	
Low (5%–15%)	5 (7.4)
Intermediate (16%–30%)	12 (17.6)
High (>30%)	44 (64.7)
Unknown	7 (10.3)
Grade	
II	17 (25.0)
III	47 (69.1)
Unknown	4 (5.9)
Primary tumour size (T)	
1	10 (18.5)
2	17 (31.5)
3	5 (9.3)
4	14 (25.9)
Unknown	8 (14.8)
Primary nodal status (N)	
0	11 (16.2)
1	16 (23.5)
2	14 (20.6)
3	8 (11.8)
Unknown	19 (27.9)
Adjuvant trastuzumab	
No	19 (27.9)
Yes	25 (36.8)
Primary metastatic disease	24 (35.3)
HER2 therapy discontinuation	
Yes	21 (30.9)
No	47 (69.1)
Site of metastases at the first occurrence	
Bone only	19 (27.9)
Lymph node metastases only	6 (8.8)
Skin only	3 (4.4)
Visceral only	13 (19.1)
Other	4 (5.9)
Multiple sites	20 (29.4)

Continued

Table 1 Continued

	n (%)
Other HER2-targeted treatments	
Lapatinib	16 (23.5)
Pertuzumab	6 (8.8)
T-DM1	2 (2.9)
Median age at diagnosis (range), years	58 (28–83)
Median survival in metastatic disease (range), months	32 (0–200)

HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtansine.

Of the patients with primary localised disease, only 57% had received adjuvant trastuzumab, since this has been a standard of care in the institute from 2006 on, and about one-third of the patients were diagnosed before that. Overall survival in cases of metastatic disease was similar to seen in previous trials with trastuzumab, with a median length of 32 months.[17–20] Median survival in our cohort of patients with metastatic disease was dramatically different among patients who had received trastuzumab as an adjuvant (16 months), who had primary metastatic disease (35 months) and who had not received trastuzumab as an adjuvant (77 months). Previous investigators have also identified absence of trastuzumab adjuvant treatment as the only indicator of long-term benefit of trastuzumab in metastatic disease.[21]

Many studies have revealed that a proportion of cases of patients with metastatic breast cancer can achieve long-term responses with trastuzumab-containing regimens. On the basis of our data, it is clear that the sensitivity of a patient to trastuzumab varies dramatically, since patients with metastatic disease who have received trastuzumab as an adjuvant and relapsed later have very poor survival compared with others. Identifying the mechanisms behind trastuzumab resistance is therefore very important and

might lead to better therapies and improved outcomes of trastuzumab-resistant patients.[22]

The most important finding in the current study is that many patients with *HER2+* can achieve long-term disease stabilisation and a HER2 treatment-free interval without rapid disease progression. In our patient cohort, HER2 therapy was discontinued in ~30% of the cases, that is, those with a long-lasting (>12 months) tumour response or with a response together with suspected severe HER2 therapy-linked side effects and later reinitiated in cases of disease progression if the severity of previous treatment-related side effects was not considered intolerable. Notably, rapid disease progression during a HER2 therapy-free interval was seldom seen in the cohort and the median duration of HER2 therapy discontinuation was 51 months. Furthermore, median survival among the patients whose HER2 therapy was discontinued was extensive compared with non-discontinued patients. Owing to the retrospective nature of the study, we are unable to predict whether survival would have been even longer with continuous HER2 therapy. However, HER2 therapy was reinitiated in only about half of the cases during the follow-up period, most (~70%) responded to therapy reinitiation and some underwent a second or even a third period of
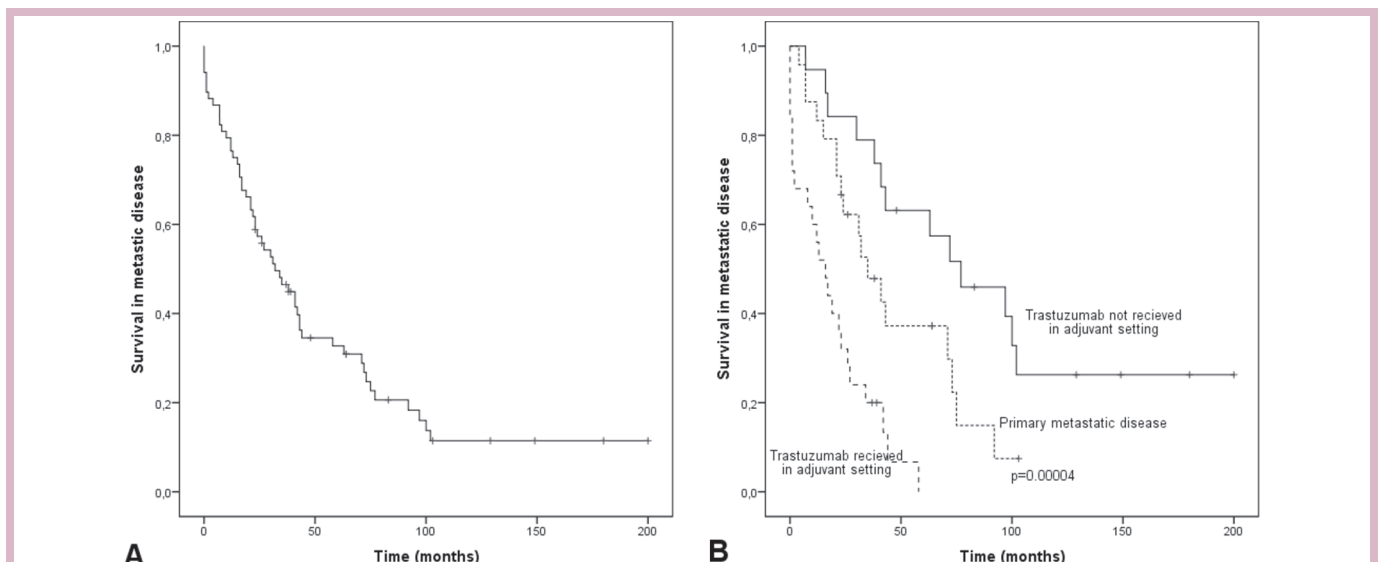

Figure 2 Kaplan-Meier estimates for survival in metastatic disease for the whole patient cohort (A) and in patients with or without history of adjuvant trastuzumab and primary metastatic disease (B). Crosses indicate censored events.

Table 2 Demographics of the patients whose HER2 therapy was discontinued or continued. NS, non-significant diference.

	HER2 therapy discontinued (n=21)	HER2 therapy continued (n=47)	p Value
	n (%)	n (%)	
Histology			
Ductal	19 (90.5)	40 (85.1)	NS
Lobular	2 (9.5)	5 (10.6)	
Unknown	0 (0)	2 (4.3)	
Oestrogen receptor status			
Positive	14 (66.7)	31 (66.0)	NS
Negative	7 (33.3)	16 (34.0)	
Progesterone receptor status			
Positive	12 (57.1)	15 (31.9)	NS
Negative	9 (42.9)	32 (68.1)	
Ki-67			
Low (5%–15%)	3 (14.3)	2 (4.3)	NS
Intermediate (16%–30%)	4 (19.0)	8 (17.0)	Low or intermediate versus high
High (>30%)	11 (52.4)	33 (70.2)	
Unknown	3 (14.3)	4 (7.9)	
Grade			
II	6 (37.5)	11 (28.9)	
III	10 (62.5)	25 (65.8)	
Unknown	0 (0)	2 (5.3)	
Primary tumour size (T)			
1	4 (19.0)	9 (19.1)	NS
2	6 (28.6)	14 (29.8)	T1–2 vs T3–4
3	5 (23.8)	3 (6.4)	
4	4 (19.0)	15 (31.9)	
Unknown	2 (9.5)	6 (12.8)	
Primary nodal status (N)			
0	5 (23.8)	6 (12.8)	NS
1	7 (33.3)	9 (19.1)	N0 vs N1–3
2	6 (28.6)	8 (17.0)	
3	0 (0)	8 (17.0)	
Unknown	3 (14.3)	16 (34.0)	

Continued

Table 2 Continued

	HER2 therapy discontinued (n=21)	HER2 therapy continued (n=47)	p Value
Distant metastases at the time of diagnosis			
0	13 (61.9)	31 (66.0)	NS
1	8 (38.1)	16 (34.0)	
Adjuvant trastuzumab			
No	12 (57.1)	7 (14.9)	p=0.0001
Yes	1 (4.8)	24 (51.1)	
Primary metastatic disease	7 (43.8)	15 (39.5)	NS
Site of metastases at the first occurrence			
Bone only	6 (28.6)	13 (27.7)	NS
Lymph node metastases only	2 (9.5)	4 (8.5)	
Skin only	1 (4.8)	2 (4.3)	
Visceral only	4 (19.0)	9 (19.1)	
Other	2 (9.5)	2 (4.3)	
Multiple sites	6 (28.6)	15 (31.9)	
Median age at diagnosis, years (range)	58.5 (40–80)	58 (28–83)	NS
Median survival in metastatic disease, months (range)	92 (21–200)	21 (0–102)	p<0.00001
Median duration of HER2 therapy before discontinuation, months (range)	15 (0–42)		
HER2 therapy discontinuation length, months	50.1 (5–124)		
Reason for trastuzumab discontinuation			
Side effects	4 (19.0)		
Prolonged response	17 (81.0)		
Depth of response before trastuzumab discontinuation			
Complete or near-complete response	8 (38.1)		
Other	13 (61.9)		
Therapy before trastuzumab discontinuation			
Trastuzumab+chemotherapy	16 (76.2)		
Trastuzumab+hormonal therapy	4 (19.0)		
Trastuzumab	1 (4.8)		

HER2, human epidermal growth factor receptor 2; NS, non-significant.
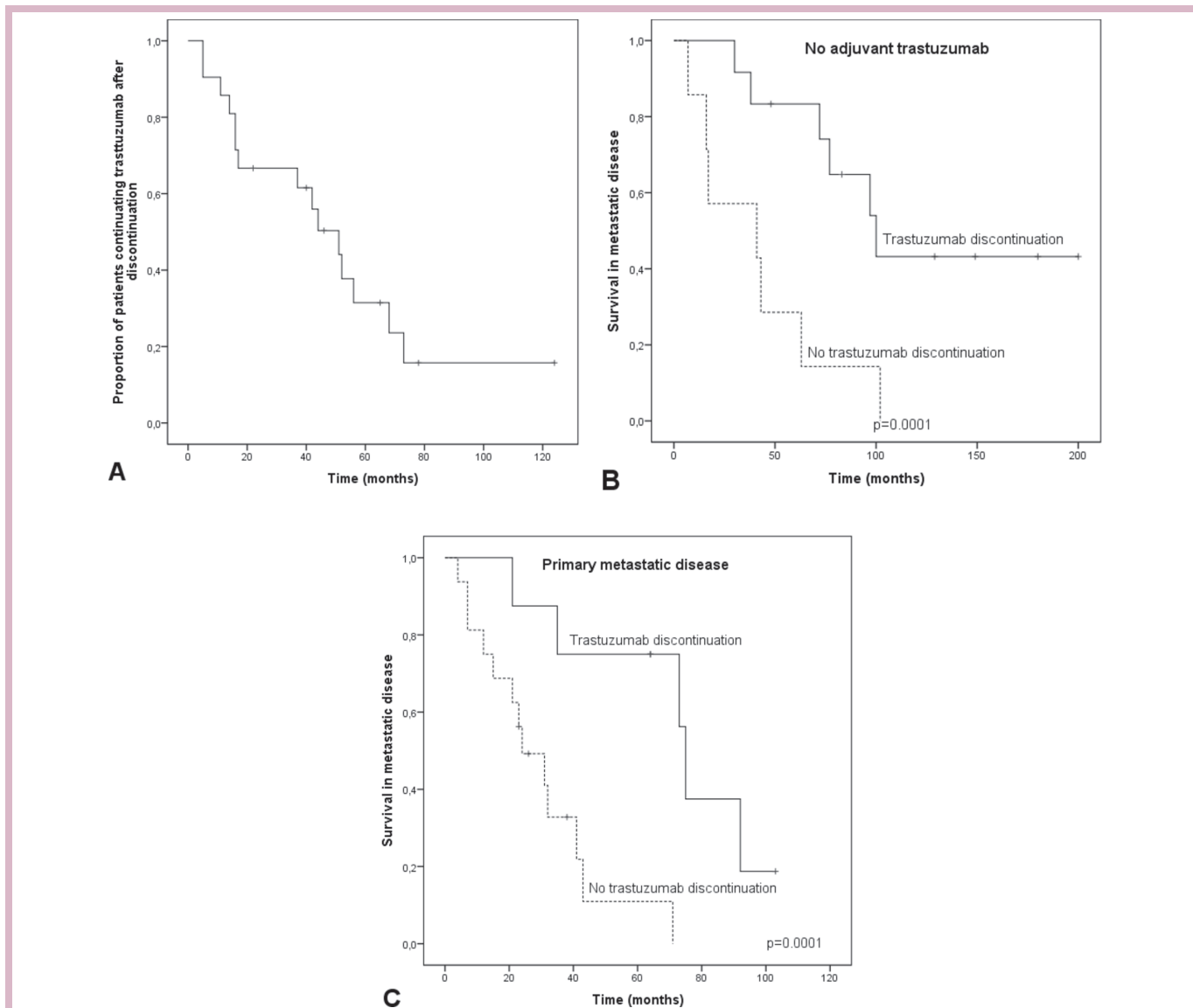
Figure 3 Kaplan-Meier estimates for trastuzumab therapy discontinuation in patients whose trastuzumab was interrupted in response or response and toxicity (A). Kaplan-Meier estimates for survival in metastatic disease for patients whose trastuzumab was continued or discontinued in patients without adjuvant trastuzumab (B) and in primary metastatic disease (C). Crosses indicate censored events.

HER2 therapy discontinuation. This might reflect that outcomes were not sacrificed in connection with HER2 therapy interruption. Previously, only case reports (one to two patients) have described patients with *HER2*-positive breast cancer remaining disease-free without further HER2 therapy after trastuzumab-containing regimens.[12 13] Even though limited in size, to our knowledge, current work describes the largest patient cohort whose HER2 therapy has been interrupted in cases of response. One-third of our cohort had OR-positive disease and some had received hormonal therapy during HER2 therapy discontinuation, which could increase the time to HER2 therapy continuation. We did not, however, see any association between receiving hormonal therapy to the HER2 therapy discontinuation length and even an inverse correlation to survival, suggesting that hormonal therapy

is not responsible to the results seen in the current work. In recent Advanced Breast Cancer consensus statement, 93% of experts agreed that optimal duration of HER2 therapy in metastatic disease is unknown in complete responders.[23] Our cohort included 38.1% of patients who had complete or near-complete response to the therapy. Complete responders had similar HER2 therapy interruption length but improved survival suggesting that depth of response could not be used as sole criteria for HER2 discontinuation.

Our work enables analysis of some predictive factors related to the opportunity to discontinue HER2 therapy. Absence of trastuzumab adjuvant treatment was the only factor associated with HER2 therapy discontinuation, a fact that has also previously been linked to prolonged trastuzumab responses.[21] Further studies on tumour

biomarker are warranted to investigate their relation to HER2 therapy-free prolonged tumour responses. High number of tumour-infiltrating lymphocytes has been previously linked to excellent disease-free numbers in patients receiving short course (9 weeks) of adjuvant trastuzumab.[24] Recent studies with T-cell-activating cancer drugs have suggested that patients whose treatment was rapidly discontinued due to adverse events can experience prolonged tumour responses.[14] Trastuzumab's dual, signal inhibitory and immunoactivating,[15 16] mode of action enables one to speculate that this would also hold true for patients treated with the agent. Prolonged treatments with HER2 agents have, however, seldom been challenged due to good tolerability of these agents and rarity of toxicity-related discontinuations.

In conclusion, we present here a retrospective, single-institute patient cohort with *HER2+* metastatic breast cancer who have been treated with HER2 antibodies. The most important finding of our work is that if HER2 therapy is interrupted in cases of a good response, patients can experience long periods without HER2 therapy.

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