CLINICAL TRIAL

Radiological complete remission in HER2-positive metastatic breast cancer patients: what to do with trastuzumab?

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Abstract

Purpose Patients with HER2-positive metastatic breast cancer (MBC) treated with trastuzumab may experience durable tumor response for many years. It is unknown if patients with durable radiological complete remission (rCR) can discontinue trastuzumab. We analyzed clinical characteristics associated with rCR and overall survival (OS) in a historic cohort of patients with HER2-positive MBC and studied the effect of stopping trastuzumab in case of rCR.

Methods We included patients with HER2-positive MBC treated with first or second-line trastuzumab-based therapy in eight Dutch hospitals between 2000 and 2014. Data were collected from medical records. We used multivariable regression models to identify independent prognostic factors for rCR and OS. Time-to-progression after achieving rCR for patients who continued and stopped trastuzumab, and breast cancer-specific survival were also evaluated.

Results We identified 717 patients with a median age of 53 years at MBC diagnosis. The median follow-up was 109 months (IQR 72-148). The strongest factor associated with OS was achievement of rCR, adjusted hazard ratio 0.27 (95% CI 0.18–0.40). RCR was observed in 72 patients (10%). The ten-year OS estimate for patients who achieved rCR was 52 versus 7% for patients who did not achieve rCR. Thirty patients with rCR discontinued trastuzumab, of whom 20 (67%) are alive in ongoing remission after 78 months of median follow-up since rCR. Of forty patients (58%) who continued trastuzumab since rCR, 13 (33%) are in ongoing remission after 68 months of median follow-up. Median time-to-progression in the latter group was 14 months.

Conclusions Achieving rCR is the strongest predictor for improved survival in patients with HER2-positive MBC. Trastuzumab may be discontinued in selected patients with ongoing rCR. Further research is required to identify patients who have achieved rCR and in whom trastuzumab may safely be discontinued.

Keywords HER2-positive · Metastatic breast cancer · Long-term survival · Radiological complete remission · Trastuzumab

Introduction

Metastatic breast cancer (MBC) is considered an incurable disease, with median overall survival (OS) for patients averaging around 34 months [1–3]. Outcome for patients with HER2-positive MBC has dramatically improved since the introduction of trastuzumab [2–6]. Radiological complete remission (rCR) is not uncommon and patients may remain in complete remission for many years [7–10]. The addition of pertuzumab to first-line trastuzumab-based therapy in HER2-positive MBC has increased median OS to 56 months [11]. Other anti-HER2 drugs, including lapatinib and trastuzumab-emtansine (T-DM1), have extended treatment options for patients with HER2-positive MBC, and patients' survival can be prolonged even further [5, 11–14].

In HER2-positive MBC patients on anti-HER2 therapy, various factors are associated with long OS such as young age (< 50 years) [15–17], good performance status [7, 15, 18], de novo metastases [7, 15, 18], no previous treatment with trastuzumab [19–21], limited tumor load (e.g.,

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oligo-metastases or single-organ metastases) [7, 17, 22], and achievement of rCR [7, 18, 23, 24]. Most studies show an association with estrogen receptor (ER)-positivity and improved survival [4, 15, 17, 24], but not all [23, 25]. What remains unsure is whether additional local treatment of metastases improves survival. Moreover, oncologists question if and when trastuzumab can be stopped after achieving rCR upon trastuzumab-based therapy [1, 26]. A survey among 44 oncologists in Canada showed that after achieving clinical or radiological CR most oncologists continue trastuzumab therapy until progression (78%) or onset of toxicity (5%) [26]. A couple of studies evaluated the effect of stopping trastuzumab in patients with HER2-positive MBC [7, 20, 27]. However, numbers were small [7], follow-up was rather short [20, 27] and not all patients had achieved CR upon trastuzumab-based therapy [20].

Therefore, our aim was to evaluate which characteristics are associated with survival and achieving rCR in patients with HER2-positive MBC treated with trastuzumab-based therapy in a historic cohort with long follow-up. Additionally, we thoroughly describe characteristics of patients with rCR, long-term outcome of patients with rCR and the effect of trastuzumab discontinuation after achieving rCR.

Materials and methods

Patients and data collection

Patients were identified from the Netherlands Cancer Registry (NCR) and linked with the institutes' tumor registries from eight Dutch hospitals (two referral and six regional hospitals). We included all patients with histologically proven HER2-positive MBC who received more than one gift trastuzumab-based palliative therapy as first or second line in one of these hospitals between January 2000 and December 2014.

Four clinicians (TS, NB, HR and CS) systematically extracted clinical characteristics from medical records using case record forms. Recorded data included date of birth, date of diagnosis of primary tumor, date of MBC, date of recurrence, tumor characteristics of the primary tumor, number and location of initial distant metastases, local ablative treatment (LAT) for metastases (surgery, radiotherapy, or radiofrequency ablation), systemic treatment for the primary tumor and for MBC, response to treatment, date of last follow-up and if death occurred the date and cause of death. The location of distant metastases was grouped into the following categories: lymph nodes (beyond locoregional), liver, lung, bone, central nervous system [(CNS); including leptomeningeal], skin and other. Oligo-MBC was defined as one to three detected metastases, not necessarily limited to a single organ. ER, progresterone receptor, and HER2-status

of the primary tumor or MBC were determined according to the Dutch guideline [29]. HER2-positivity was defined as an immunohistochemistry score of 3+ or 2+ and amplification measured by in situ hybridization [28]. ER and progesterone receptor positivity was defined as ≥ 10% positive nuclear staining [29, 30]. The first chemotherapy or targeted therapy administered for MBC was defined as first-line therapy for MBC. The next therapy that was started following disease progression was defined as second-line therapy. Subsequent lines were counted in this manner. Progression was defined as either progression detected on radiological imaging assessed by local radiologist or clinical deterioration most likely caused by MBC. Radiologic response was assessed during routine follow-up by local radiologists. Radiologic complete response was defined as no-evidence-of-disease (NED) on radiological examination of the previously detected metastases (either contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging, or [18F]-fluorodeoxyglucose (FDG) positron emission tomography-CT) upon systemic treatment. Bone metastases were classified as rCR if metabolic activity normalized compared to start, seen on either FDG-PET-CT or bone scintigraphy. Patients who received successful LAT (i.e., NED after local treatment) for their metastases without rCR upon systemic treatment were not classified as having achieved rCR upon systemic therapy. Follow-up scans were performed at discretion of the treating physician in line with institutional guidelines.

Statistical analyses

The primary endpoint was OS, defined as date of diagnosis of MBC until death from any cause or last follow-up [31]. For patients last known to be alive, OS data were censored at the time of last follow-up visit. Breast cancer-specific survival (BCSS), defined as date of diagnosis of MBC until death from breast cancer or last follow-up, was a secondary outcome. Follow-up time was calculated with the reverse Kaplan–Meier method. Cox-proportional hazard models were used to identify prognostic factors for survival. Kaplan–Meier survival estimates were calculated for patients with and without the most important prognostic factor according to the Cox-model and compared with the log-rank test. We explored characteristics of patients who continued and patients who stopped trastuzumab after achievement of rCR. As date of radiological evaluation was not standardized, the time to achieve rCR that was recorded does not adequately represent the time actually needed to achieve rCR. We therefore used logistic regression rather than proportional hazard models to identify factors associated with higher odds of achieving rCR. Hazard ratios (HR) and odds ratios (OR) are given with their corresponding 95% confidence intervals (CI). Factors with a P value < 0.10 for

univariable associations with outcomes were included in the multivariable models. *P* values < 0.05 were considered statistically significant; all tests were two-sided. Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Figures were generated using Graph Pad Prism 5.0 (Graph Pad Software, La Jolla, CA, USA).

Results

Patient characteristics

Seven hundred fifty-eight patients who received trastuzumab for MBC were identified and 717 patients were included in the final analysis. Reasons for exclusion were no trastuzumab as first- or second-line treatment for MBC (*n* = 21), only one cycle of trastuzumab received (*n* = 11), diagnosis of another cancer that determined prognosis (*n* = 4) and incompleteness of data (*n* = 5) (Supplementary Figure 1). Patient and tumor characteristics are shown in Table 1. Median age at diagnosis of MBC was 53 years (interquartile range [IQR] 46-61). One-hundred forty-three (20%) patients were diagnosed with oligo-MBC. Median time from breast cancer diagnosis until MBC was 26 months (IQR 0-56), and 194 patients (27%) were diagnosed with de novo metastases. In total, 595 patients (83%) had not received trastuzumab previously. Five-hundred fifteen patients (72%) received trastuzumab as first-line treatment for MBC.

Survival and predictive factors

After 109 months (IQR 72-148) of median follow-up, 579 patients had died, of whom 566 (98%) were due to MBC. The median OS for all patients was 37 months (IQR 21-72). Achievement of rCR had the strongest impact on death; adjusted HR of 0.27, 95% CI 0.18–0.40 (Table 2). Other factors significantly associated with longer OS in multivariable regression analysis were: longer interval from breast cancer diagnosis until MBC, ER-positivity, single-organ metastases, no neoadjuvant/adjuvant trastuzumab, de novo MBC, successful LAT of metastases. Liver, brain, and skin metastases showed a significant unfavorable association with OS. Analyses for BCSS were in line with OS data (data not shown).

Achievement of rCR

Seventy-two patients (10%) achieved rCR, of whom 42 (58%) are alive at last follow-up. The median OS for patients who achieved rCR was 142 months (11.8 years) (IQR 61-not reached) compared to median OS of 35 months (IQR 19-61 months) for patients who did not achieve rCR (*p* value < 0.001, Fig. 1). The 10-year OS estimate for patients

who achieved rCR was 52% compared to 7% for patients who did not achieve rCR (Fig. 1). Sixty-six patients achieved rCR upon treatment with trastuzumab combined with chemotherapy, four upon endocrine treatment combined with trastuzumab and two upon endocrine treatment only.

Clinical characteristics at diagnosis of MBC independently associated with a higher chance to achieve rCR were oligo-metastases (adjusted odds ratio [aOR] 4.19, 95% CI 2.22–7.94), and de novo MBC (aOR 5.14, 95% CI 2.01–13.18). Patients who received trastuzumab as second-line treatment had significantly lower chance to achieve rCR (aOR 0.26, 95% CI 0.12–0.57, Table 3).

The effect of discontinuation of trastuzumab after achieving rCR

Thirty patients (43%) discontinued trastuzumab after achieving rCR. The median time from onset of rCR to discontinuation was 6 months (IQR 0-9). Twenty patients (67%) who stopped trastuzumab after rCR remain in complete remission, with a median follow-up of 78 months (IQR 60-100) since onset of rCR. Eight patients (27%) who stopped trastuzumab after rCR experienced disease progression with a median time-to-progression (TTP) of 15 months (IQR 10-18) since last gift of trastuzumab. In five patients with disease progression after rCR trastuzumab was restarted. Four patients experienced stable disease for median time of 23 months since restart of trastuzumab. One of these patients achieved a new rCR upon trastuzumab-based therapy and is in ongoing remission at last follow-up with ongoing trastuzumab-based therapy (Fig. 2). From the twenty patients who remain in rCR since discontinuation of trastuzumab, metastatic lesions were pathologically proven at diagnosis of MBC in eight.

Forty patients (58%) continued trastuzumab treatment after achieving rCR. Of them, 13 (33%) are in ongoing remission after 68 months (IQR 44-107) of median follow-up. Median TTP was 14 months (IQR 6-27).

In the group of patients who stopped trastuzumab, more patients were diagnosed with oligo-metastases and received LAT for the primary tumor and metastases (not formally tested; Supplementary Table 1).

Discussion

Trastuzumab has dramatically improved survival for patients with HER2-positive MBC with some patients surviving over 10 years. Our multicenter analysis in > 700 patients treated with trastuzumab-based systemic therapy for HER2-positive MBC shows that patients who achieve rCR have a very favorable prognosis compared to patients without rCR. Other factors associated with improved outcome are de novo MBC,

Table 1 Baseline characteristics

Clinical and pathological characteristics	All patients (N=717)
Age at diagnosis MBC, years	
Median (IQR)	53 (46–61)
Time until MBC, months	
Median (IQR)	26 (0–56)
De novo MBC, no. (%)	
De novo MBC	194 (27)
Metachronous MBC	523 (73)
ER-status at diagnosis, no. (%)	
ER-positive	399 (56)
ER-negative	316 (44)
Single-organ metastases, no. (%)	
Single-organ metastases	329 (46)
More organs metastases	388 (54)
Oligo-metastases (≤ 3 metastases), no. (%)	
Oligo-metastases	143 (20)
Multiple metastases	562 (80)
Location of metastases at diagnosis MBC, no. (%)	
Bone	395 (55)
Liver	280 (39)
Lymph nodes	260 (36)
Lung	233 (33)
Skin	50 (7)
CNS	35 (5)
Prior neoadjuvant/adjuvant trastuzumab, no. (%)	
Yes	123 (17)
No	595 (83)
Moment first trastuzumab for MBC, no. (%)	
Trastuzumab received in 1st line	515 (72)
Trastuzumab received in 2nd line	202 (28)
First-line treatment, no. (%)	
Trastuzumab + taxanes	303 (42)
Trastuzumab + vinorelbine	91 (13)
Trastuzumab + capecitabine	24 (3)
Trastuzumab + other	29 (4)
Trastuzumab + endocrine therapy	30 (4)
Trastuzumab monotherapy	16 (2)
Trastuzumab + pertuzumab + CT	22 (3)
Successful local ablative treatment of metastases, no. (%)	
Yes	60 (9)
No	647 (90)
Achievement of rCR, no. (%)	
rCR achieved	72 (10)
rCR not achieved	645 (90)

MBC metastatic breast cancer, *IQR* interquartile range, *ER* estrogen receptor, *CNS* central nervous system, *rCR* radiological complete remission

% is based on known values

longer interval from breast cancer diagnosis until MBC, single-organ metastases, ER-positivity, no liver metastases, no brain metastases, no skin metastases, no prior adjuvant treatment with trastuzumab and successful LAT of metastases.

Patients in our cohort are similar to patients with HER2-positive MBC in other multicenter cohorts [7, 15, 16]. Outcome for patients in our cohort in terms of median OS (37 months) and probability to achieve rCR (10%) are also

Table 2 Adjusted hazard ratios for death—multivariable Cox regression analyses

	Adjusted HR	95% CI	P value
Time until MBC	0.99	0.99–0.99	0.001
ER-positive	0.70	0.59–0.84	< 0.001
Oligo-metastases (≤ 3 metastases)	0.85	0.64–1.12	0.242
Single-organ metastases	0.73	0.59–0.90	0.003
Liver metastases	1.34	1.10–1.62	0.003
Lung metastases	0.99	0.82–1.20	0.890
Skin metastases	1.59	1.16–2.16	0.003
CNS metastases	1.63	1.08–2.46	0.020
Prior neoadjuvant/adjuvant trastuzumab			
Prior trastuzumab	1		
No neoadjuvant/adjuvant trastuzumab	0.60	0.47–0.76	< 0.001
No prior trastuzumab—de novo MBC	0.42	0.31–0.57	< 0.001
Radiologic complete remission	0.27	0.18–0.40	< 0.001
Successful local ablative treatment of metastases	0.49	0.31–0.78	0.002

HR hazard ratio, *CI* confidence interval, *MBC* metastatic breast cancer, *ER* estrogen receptor, *rCR* radiological complete remission

Multivariable Cox regression analysis, values are adjusted for all other variables. Selection of variables is based on statistically significant variables ($p < 0.10$) in univariable models
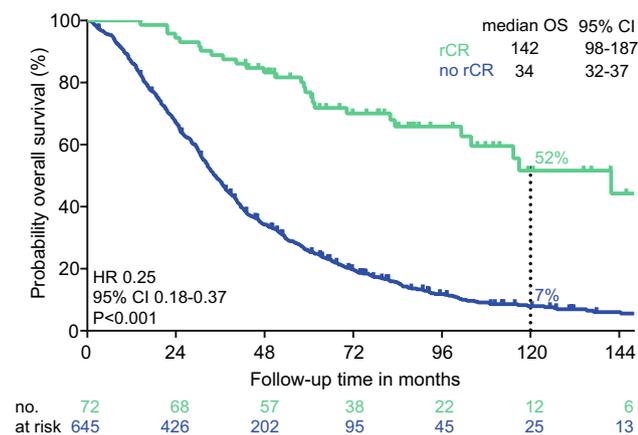
Fig. 1 Probability of overall survival after diagnosis of metastatic breast cancer for patients who achieved radiologically complete remission and patients who did not. *rCR* radiologically complete remission, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval. HR based on univariable analysis

comparable to other cohorts [7, 17, 24, 25]. With first-line dual HER2-blockade for all patients diagnosed with HER2-positive MBC today, the percentage of patients achieving rCR may increase.

Patients and oncologists are reluctant to stop treatment and generally continue trastuzumab even if rCR is achieved; thereby accepting frequent hospital visits, possible toxicity, and associated drug costs. If the disease is in definitive remission or controlled by immune surveillance, consolidation treatment might no longer be necessary. Whether and when trastuzumab could be discontinued without

compromising prognosis is a matter of a clinical debate that is unfortunately not yet supported by randomized-controlled trial data [7, 18, 26, 27, 32]. Among the 70 patients in our cohort who achieved rCR upon trastuzumab-based treatment, 30 (43%) discontinued trastuzumab after rCR at the discretion of the treating physician. Most patients discontinued trastuzumab after completing one-year trastuzumab treatment since diagnosis of MBC or ongoing remission upon systemic treatment. Of them, 20 (67%) remain disease-free for several years and another two patients died due to another cause than breast cancer while being in remission. In patients who experienced progression after discontinuation of trastuzumab, trastuzumab was restarted in five, resulting in rCR in one patient and stable disease in four patients. Based on our data we cannot draw conclusions whether all patients who achieve rCR should continue trastuzumab or not. To optimally answer this important question, patients should be randomly allocated to either continuation or discontinuation. However, as such a study is unlikely to be performed, a validation of our findings in an independent prospective cohort of patients who have achieved rCR can strengthen our findings.

In our cohort patients with oligo-MBC (≤ 3 metastases) or de novo MBC were most likely to achieve rCR. Wong and colleagues [24] also found that a few metastatic sites (1-3) was associated with achieving NED in a cohort of HER2-positive de novo MBC. However, the definition of NED they used is slightly different from what we classified as rCR as patients could also achieve NED after surgery of metastases, which is more often performed in patients with few (oligo-) metastases. LAT for metastases in patients with

Table 3 Adjusted odds ratios for achieving radiological complete remission

	Adjusted OR	95% CI	P value
ER-positive	0.87	0.51–1.52	0.638
Oligo-metastases (≤ 3 metastases)	4.19	2.22–7.94	< 0.001
Single-organ metastases	0.97	0.49–1.93	0.938
Bone metastases	0.42	0.23–0.77	0.005
Liver metastases	0.54	0.28–1.04	0.066
Lung metastases	0.55	0.28–1.08	0.082
Prior trastuzumab			
Prior trastuzumab	1	–	–
No adjuvant trastuzumab	2.80	1.13–6.93	0.026
No prior trastuzumab—de novo MBC	5.14	2.01–13.18	0.001
Trastuzumab second line	0.26	0.12–0.57	0.001

OR odds ratio, *CI* confidence interval, *MBC* metastatic breast cancer, *ER* estrogen receptor

Multivariable logistic regression analyses, values are adjusted for all other variables. Selection of variables is based on statistically significant variables ($p < 0.10$) in univariable models
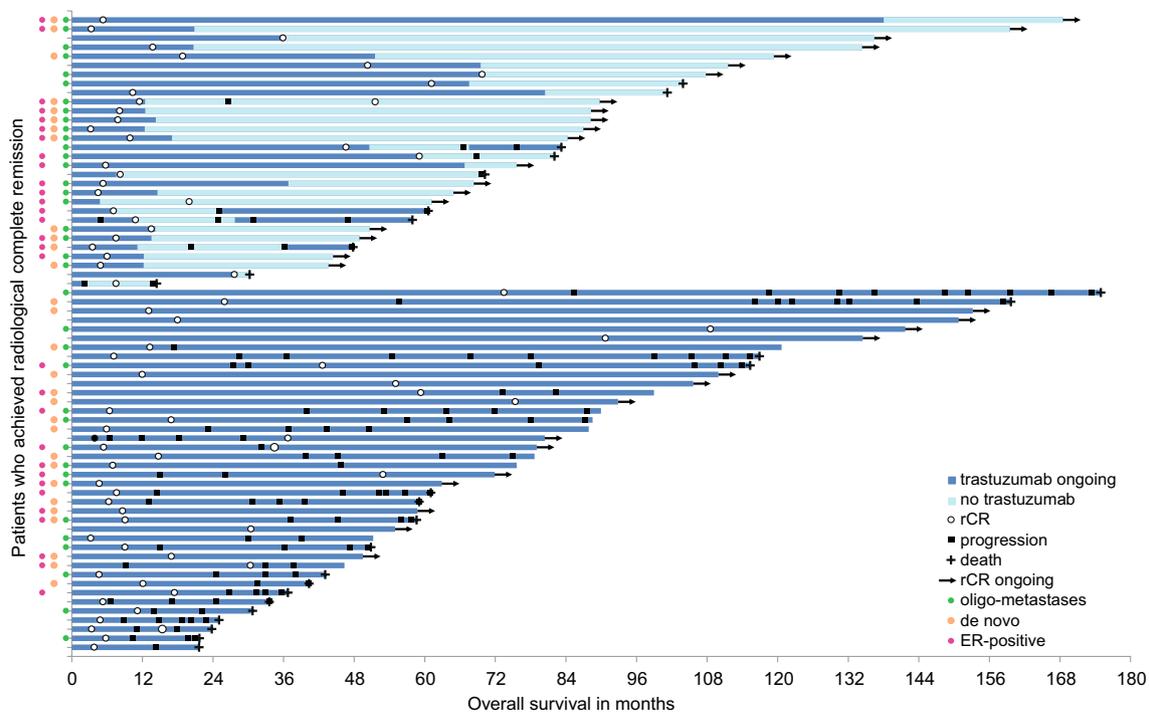
Fig. 2 Swimmers plot all patients who achieved radiological complete remission upon trastuzumab-based treatment ($n = 70$). *MBC* metastatic breast cancer, *rCR* radiological complete remission, *ER* estrogen receptor. Two patients achieved rCR upon hormonal treatment and are not included in this figure

few metastases was significantly associated with improved survival in our multivariable analysis. Harano and colleagues [33] also observed improved survival after local treatment of metastases.

Patients with skin metastases at MBC diagnosis have a worse OS compared to patients with visceral, bone or CNS metastases. To the best of our knowledge this has not been described before.

There are some limitations that have to be considered when interpreting our results. Firstly, our cohort involves historic data and data collection was not prospectively planned, which may have caused incomplete data or information bias. Secondly, HER2-status was based on assessment at time of initial breast cancer diagnosis, which does not necessarily correspond to HER2 status of the metastatic lesions. Ten percent discordance for HER2-status between

primary tumor and metachronous metastases has been reported [34]. Thirdly, analysis regarding LAT for metastases and rCR can be subject to selection bias and immortal-time bias [35]. Most patients who received local treatment of metastases are selected based on remarkable or durable response. Treatment with a multimodality approach, including LAT for metastases, for patients with oligo-MBC was used in some but not all institutes; this variation might have influenced results. Additionally, patients who underwent LAT of metastases did clearly not die before they underwent LAT, resulting in a biased longer survival time for this group. Fourthly, part of the patients in our cohort ($n = 405$, 77%) diagnosed with metachronous MBC did not previously receive neoadjuvant or adjuvant trastuzumab, while currently almost all patients who develop metachronous metastases receive neoadjuvant or adjuvant trastuzumab. In our analysis and in previous studies response to treatment and outcome is different in patients who have received prior trastuzumab [19]. As the majority of patients with metachronous MBC did receive trastuzumab in the neoadjuvant or adjuvant setting, we think our data are important for today's HER2-positive MBC patients. Lastly, only 22 patients (3%) in our cohort received dual HER2-targeted therapy, which is the current standard of care for patients with HER2-positive MBC. Despite these limitations, with a unique long follow-up of this multicenter cohort, we were able to confirm clinical characteristics associated with improved survival.

Conclusion

This large multicenter cohort of 717 patients with HER2-positive MBC shows that achieving radiologic complete remission has important prognostic value. The 10-year OS estimate for patients who achieved rCR was 52 versus 7% for patients who did not achieve rCR. These findings support a treatment strategy that increases the likelihood of achieving rCR and thus optimizing the chance for long-term survival. However, strong treatment recommendation cannot be made in view of the observational nature of the data. Decisions to discontinue trastuzumab in case of rCR should be carefully considered between physician and patient until more research has been performed.

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Compliance with ethical standards

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