Long-responders to anti-HER2 therapies: A case report and review of the literature

LUCA CANTINI, MIRCO PISTELLI, AGNESE SAVINI, LUCIA BASTIANELLI, ARIANNA DELLA MORA, FILIPPO MERLONI, MICHELA BURATTINI and ROSSANA BERARDI

Medical Oncology, Marche Polytechnic University, University Hospital Ospedali Riuniti Ancona, I-60126 Ancona, Italy

Received May 30, 2017; Accepted November 7, 2017

DOI: 10.3892/mco.2017.1495

Abstract. Since the introduction of targeted therapies, prognosis in human epidermal growth factor receptor (HER) 2-positive metastatic breast cancer (MBC) has radically changed. The addition of Pertuzumab to Trastuzumab and standard chemotherapy has further increased patients' overall survival (OS). However, there is no agreement regarding the optimal duration of trastuzumab therapy in selected patients achieving long-term complete remission. In addition, no potential factors of long-term benefit have been identified yet. In the present study, we report the case of a MBC woman who was successfully treated with trastuzumab for over 10 years. At the time of diagnosis (February 2005), she revealed lung, nodal and bone metastases. Therefore, a first-line chemotherapy with Epirubicine and Docetaxel was administered for 6 cycles and then the patient started Trastuzumab plus hormonal therapy until reaching a sensible reduction of mammary lump and disappearance of distant metastases. Following a multidisciplinary evaluation, in November 2006, the patient underwent radical mastectomy and axillary dissection, achieving a complete remission. She continued Trastuzumab until September 2015 (for a total of 156 cycles) when a pleural diffusion was demonstrated. Long-term survival during anti-HER2 treatment remains a rare and optimal situation. Currently, no data exist to support trastuzumab interruption in this setting and collaborative efforts to better analyze the characteristics of long-responder patients are needed. Data regarding prognostic factors in this setting are relatively confusing. Our review reveals that hormonal receptor (HR)-positive disease is associated with a better prognosis, whereas the role of visceral spread differs by single or dual target anti HER2-inhibition. The introduction of Pertuzumab is raising concerns in terms of toxicity and its cost effectiveness. While waiting for novel molecular data and randomized trials, available evidence advocates continuous use of anti-HER2 therapies until disease progression or development of side effects.

Correspondence to: Dr Luca Cantini, Medical Oncology, Marche Polytechnic University, University Hospital Ospedali Riuniti Ancona, via Conca 71, I-60126 Ancona, Italy
E-mail: lucacantini.med@gmail.com

Abbreviations: MBC, metastatic breast cancer; OS, overall survival; CHT, chemotherapy; LTS, long-term survival; PFS, progression-free survival; HR, hormonal receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; TILs, tumor-infiltrating lymphocytes; CT, computer tomography; CEA, carcino-embryonic antigen; Ca 15.3, cancer antigen 15-3; PET, positron emission tomography; TDM-1, ado-trastuzumab emtansine; CI, confidence interval; CR, complete response; PR, partial response; HR, hazard ratio; aHR, adjusted hazard ratio; OR, odds ratio; TTP, time to progression; LVEF, left ventricular ejection fraction; DCR, durable complete response; SD, stable disease

Key words: breast cancer, HER2, trastuzumab, pertuzumab, long-term survival, maintenance

Introduction

Human epidermal growth factor receptor 2 (*HER-2*) gene is amplified or overexpressed in 10-34% of breast cancers (1). Historically, HER2-amplified metastatic breast cancer (MBC) is an aggressive cancer subtype although trastuzumab has changed the natural history of the disease. In the first-line setting, Trastuzumab, associated with chemotherapy, has shown an improvement of the outcome, compared to standard chemotherapy, in terms of progression-free survival (PFS) and overall survival (OS). Since the publication of initial data on trastuzumab in 2001 by Slamon *et al* (2), patient outcome has shown improvement from 7.4 months of PFS and 25 months of OS up to 18 months and 56.5 months (3), respectively, in the CLEOPATRA trial (4) by the addition of a new targeted agent (pertuzumab) to trastuzumab and standard chemotherapy.

After the introduction of anti-HER2 therapy, OS of hormonal receptor (HR)-negative/HER2-positive disease is longer than that of HR-negative/HER2-negative (5). Despite the improvements, only few patients experienced a sustained and prolonged response and the majority of them had a progression of HER2-positive disease within 2 years (6). Some cases of prolonged complete response of HER2-amplified MBC have been reported as a consequence of treatment with trastuzumab (7,8) but up to now the real frequency of durable remissions is not assessable. In addition, we lack specific evidence about the optimal duration of anti-HER2 maintenance therapy, later cardiotoxicity and costs-associated with anti-HER2 therapies in longest responsive patients.

Hereby, we report the case of a woman with a primary HER2-positive MBC who experienced a durable complete response with trastuzumab treatment.

Case report

A 53-year-old caucasian woman with negative family history presented in January, 2005 with a nodule of approximately 10 cm in the upper central quadrant of her right breast, associated with skin retraction and ulcer. A 2 cm fixed lymphadenopathy in the right axilla was also noted. A core biopsy revealed a ductal carcinoma, grading 2, with positive estrogen receptor (ER) (75%) and progesterone receptor (PR) (13%); HER-2 was overexpressed (3+). No tumor-infiltrating lymphocytes (TILs) were detected (TILs value resulted 0%). The computer tomography (CT) of chest and abdomen performed in February, 2005 revealed lung metastases, mediastinal lymphonodal enlargement and a lytic localization on L1 vertebra, later confirmed by bone scintigraphy. Clinical TNM stage was cT4cN2M1. Carcino-embryonic antigen (CEA) and cancer antigen 15-3 (Ca 15.3) were 5,9 ng/ml and 38 U/ml, respectively. The baseline echocardiography did not exhibit any signs of cardiomyopathy, and the ejection fraction was good (70%).

In the same month, the patient started a first-line chemotherapy (CHT) with Epirubicine (75 mg/mq on day 1) and Docetaxel (80 mg/mq on day 1) every 3 weeks. After 3 cycles a clinical response was shown: the lesion was already improving, the skin ulcer started healing and axillary lymph nodes shrinking. Thus, the patient continued chemotherapy for a total of 6 cycles and then began Letrozole (2,5 mg daily) plus Trastuzumab (8 mg/kg first dose and then 6 mg/kg every 3 weeks) aiming to maintain the clinical remission. Prior to starting Trastuzumab (June, 2005), the CT scan confirmed a slightly reduction of the mammary lump while lung metastases were stable. In February, 2006 the disease was stable, while later in June, 2006, lung lesions were disappeared and glucose uptake in the right mammary gland was decreased, as shown by the positron emission tomography (PET) scan. After a multidisciplinary evaluation, in November 2006, the patient underwent radical mastectomy and axillary dissection. Pathologic examination revealed multicentric mammary carcinoma and diffuse regressive aspects due to pre-operative treatments. TILs value was 4%. The neoplasm still involved nipple and breast cutis. One out of 10 recessed lymph nodes was positive. After surgery, the patient continued Letrozole (2,5 mg daily) plus Trastuzumab 6 mg/kg i.v. every 3 weeks. She continued her follow up performing PET/CT scan every 6 months for the first 3 years, then annually. During the treatment, she periodically performed echocardiography (every 3-6 months) to monitor the potential cardiotoxicity of the biological drug but no sign of cardiomyopathy was revealed and the ejection fraction maintained an excellent value (60-65%). No signs of relapse or adverse events were identified except for myalgia and morning stiffness related to hormonal treatment. Globally, 156 cycles of Trastuzumab were administered and she received the drug for >10 years.

In January 2015, CEA started increasing and a CT scan performed in February pointed out several nodular lesions <1 cm on diaphragmatic, parietal and fissural pleural. These findings were still stable at imaging in May 2015 although CEA continued to raise up. Therefore, the patient continued Trastuzumab and Letrozole strictly monitoring the evolution of disease. In September 2015, progression was undeniable: Pleural lesions were increased in size and numbers. Consequently, Trastuzumab was stopped and a new line of treatment with ado-trastuzumab emtansine (TDM-1) was proposed. At first CT (December 2015) scan evaluation, thoracic nodules showed a partial response and the patient continued treatment without experiencing any adverse events. In July 2016, the CT scan revealed progression of the disease in mediastinal pleura. Suspected epiphrenal lymphoadenopaties were also documented. The patient underwent a 3rd line treatment with Lapatinib plus Capecitabine and the last total body CT scan (December 2016) confirmed stable disease. Table I summarizes the patient's medical history.

Discussion

In the present study, we report the case of a patient who experienced a PFS of 10 years and achieved a durable complete response with Trastuzumab and endocrine therapy as maintenance after first-line chemotherapy. In the literature, there are only a few published case reports of long survival rates in Trastuzumab-treated patients (7,9-13). This may be due to the fact that the majority of patients experience progression of disease within two years and the percentage of durable remissions remains unknown (6).

In responsive patients, available guidelines (both from the European Society for Medical Oncology and the American Society of Clinical Oncology) (14-16) and current clinical practice support continue to target HER-pathway until disease progression or development of side effects. Treatment with anti-HER2 drugs remains the standard of care but there is not a strong agreement on how long it should be maintained in HER2-positive MBC patients after obtaining a complete response.

Patients enrolled in the CLEOPATRA trial were exposed to the combination of pertuzumab and trastuzumab for a median time of 18.1 months and to trastuzumab alone for 11.8 months (6).

Recently, Yeo *et al* retrospectively evaluated 215 patients with HER2-positive, locally advanced or metastatic disease who were given a first-line therapy with Trastuzumab between 2001 and 2010 at Royal Marsden Hospital (17). The median PFS was 12 months (95% CI: 10.3-14.6 months) consistent with that seen in the control arm with docetaxel plus trastuzumab in the CLEOPATRA trial, although only 58% received trastuzumab combined with chemotherapy. The median OS reached 2.6 years (95% CI: 2.2-3.3). Seventeen (8%) complete responses (CR) and 120 (57%) partial responses (PR) were observed. One-hundred three (48%) patients continued trastuzumab without any signs of progression beyond 1 year achieving a median PFS of 2.5 years, while 59 (27%) of the 103 patients continued beyond 2 years and the median PFS was 4.9 years. One half of 59 patients who were responding at 2 years, were still in remission at 5 years.

Similarly, Witzel *et al* (18) analyzed patients with non-progressive disease for at least 2 years after diagnosis of inoperable locally recurrent or MBC under continuous Trastuzumab therapy. Data were collected by the HER-OS

Table I. Patient medical history.

Treatment line	Start and stop (year/month)	Sites of disease	Therapeutic schedule	Best response	TTP (months)
1st	From 2005/02 to 2005/06	Local, lung, nodes, bone	Epirubicin (75 mg/mq day 1) and Docetaxel (80 mg/mq day 1) w3	PR	127
1st (maintenance)	From 2005/06 to 2015/09	Local, lung	Letrozole (2.5 mg daily) and Trastuzumab (8 mg/kg first dose day 1 and then 6 mg/kg day 1 w3)	CR	
2nd	From 2015/09 to 2016/07	Pleura	TDM-1 3.6 mg/kg w3	PR	10
3rd	From 2016/08 up to now	Pleura, nodes	Lapatinib (1,250 mg daily) and Capecitabine (1,000 mg/mq b.i.d. from days 1 to 14 w3)	SD	Ongoing

TTP, time to progression; PR, partial response; CR, complete response; SD, stable disease; TDM-1, ado-trastuzumab emtansine.

database, a German online documentation platform for patients with advanced HER2-positive. In this subset, median time to progression was 4.5 years (95% CI: 4.0-6.6 years) and 47.1% of patients (95% CI: 39.9-54.1%) remained in remission for >5 years.

Prognostic and predictive factors on anti-HER2 treatment. Undoubtedly, targeted therapy radically changed the history of HER2-amplified MBC, improving the prognosis of women. However, HER2-positive breast cancer represent a heterogeneous disease with different behavior patterns. Several studies have attempted to identify prognostic factors in this setting of patients to determine favorable long-term outcomes (Table II).

A retrospective analysis from the CLEOPATRA trial led to an association between TILs values and improved prognosis. Each 10% increase in stromal TILs suggested a significant benefit in terms of OS (adjusted HR 0.89, 95% CI: 0.83-0.96, P=0.0014) (19).

In the Royal Marsden experience, no parameters were found to predict for long-term outcome (17). Patients who achieved a CR showed a trend towards improved PFS (HR 0.60, 95% CI: 0.37-1.12, P=0.065).

In a multicenter, prospective, observational, cohort study of 1,023 patients with HER2-positive metastatic disease (RegistHER), 404 patients experienced long-term survival (LTS), defined as survival >36 months from metastatic diagnosis. Factors associated with longer OS included ER- or PR-positive disease, metastasis to bone only or bone plus breast or node/local sites, first-line trastuzumab use and first-line taxane use (20).

According to another review of case reports presented by Ihnenfeld *et al*, prolonged remissions were indeed more frequent in patients with hormone-receptor negative disease and liver metastases (11).

Harano *et al* (21) recently collected data from 1,063 patients with HER2+ MBC diagnosed between 1994 and 2012 and treated with anti-HER2 therapy. They identified 154 (14.5%) patients categorized as long-term survivors (OS ≥5 years), whose median OS was 92.2 months. Hormone receptor positivity (OR 1.69; 95% CI: 1.17-2.44), resection of metastases (OR 2.38; 95% CI 1.53-3.69), and primary breast surgery in patients with *de novo* stage IV (OR 2.88; 95% CI 1.47-5.66) was associated with improved LTS.

In a series of 217 patients with HER2-positive metastatic disease presented by Fiteni *et al* (22), 56 (26%) survived >5 years and the median disease-free interval was 17 months. Seventy per cent of these long-survivors were hormone receptor-positive and all complete responders were given a taxan-based chemotherapy in combination with Trastuzumab. In multivariate analysis, the only factors that remained significant were treatment in specialized hospital (aHR 0.78; 95%CI: 0.64-0.94; P=0.03) and age inferior to 50 (aHR 0.76; 95%CI: 0.59-0.95, P=0.02).

Discontinuation of anti-HER2 drugs. The rate of patients who survived for ≥5 years was higher in a retrospective, single-institution review of 168 patients with HER2-positive MBC by Murthy *et al* (33%, 56 out of 168 patients) , of whom 12 (7%) were even considered 'exceptional responder' because they reached an overall survival >10 years (23). In this cohort, younger age at diagnosis, hormone receptor positive status and only having one organ involved at diagnosis were found to be associated with better prognosis. Four patients with MBC discontinued Trastuzumab and continued without any cancer-directed therapy for a median of 7.4 years (range, 0.2-12.0). This observation suggests that discontinuation of Trastuzumab may be safely taken into account in some patients, who may have been treated successfully.

On the contrary, the analysis conducted by Witzel *et al* (18) found that interruption of Trastuzumab in complete responder patients was associated with shorter TTP (P=0.0005).

Hsieh *et al* (13) recently described the case of a woman who underwent systemic therapy with paclitaxel (80 mg/mq weekly) and trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly). Globally, only 5 doses of paclitaxel were administered due to toxicity. At week 8 of trastuzumab, a CT scan revealed near complete disappearance of pulmonary and liver metastases. Thus, it was decided to continue with a 3-weekly trastuzumab

Table II. Univariate and multivariate analysis of prognostic factors significantly associated with overall survival in patients treated with anti-HER2 therapies.

Authors, year	Drugs	Patients (n)	Predictive/prognostic factor	Association with OS	(Refs.)
Swain *et al*, 2015	Trastuzumab plus pertuzumab arm (compared to Trastuzumab alone)	808	TILs	HR 0.89, 95% CI: 0.83-0.96, P=0.0014	(25)
			Visceral disease	HR 0.59, 95% CI: 0.48-0.74, P=0.03	
			Non-visceral disease	HR 1.11, 95% CI: 0.66-1.85, P=0.03	
Yardley *et al*, 2014	Trastuzumab	1,001	HR-positive disease	HR 0.62, 95% CI: 0.45-0.86, P=NA	(20)
			Metastases to bone only or bone+breast only	HR 0.92, 95% CI: 0.58-1.44, P=NA	
			Metastases to node/local	HR 0.55, 95% CI: 0.38-0.82, P=NA	
			First-line taxane use	HR 0.63, 95% CI: 0.45-0.88, P=NA	
Harano *et al*, 2016	Trastuzumab and/or lapatinib	1,063	HR-positive disease	OR 1.69, 95% CI: 1.17-2.44, P=0.005	(21)
			Resection of metastases	OR 2.38, 95% CI: 1.53-3.69, P<0.001	
			Primary breast surgery in patients with *de novo* stage IV	OR 2.88, 95% CI: 1.47-5.66, P=0.002	
			Visceral metastases	OR 0.61, 95% CI: 0.40-0.91, P=0.016	
			≥3 metastatic sites	OR 0.41, 95% CI: 0.23-0.72, P=0.019	
Fiteni *et al*, 2014	Trastuzumab	217	Treatment in specialized hospital	aHR 0.78, 95% CI: 0.64-0.94; P=0.03	(22)
			Age <50 years	aHR 0.76, 95% CI: 0.59-0.95, P=0.02	
Murthy *et al*, 2016	Trastuzumab or lapatinib	168	Age (continuous variable)	HR 1.02, 95% CI: 1.01-1.04, P=0.005	(23)
			Multi-organ involvement	HR 1.78, 95% CI: 1.12-2.84, P=0.027	
			HR-positive disease	HR 0.66, 95% CI: 0.45-0.97, P=0.032	

TILs, tumor-infiltrating lymphocytes; OS, overall survival; HR, hazard ratio; aHR, adjusted hazard ratio; OR, odds ratio; CI, confidence interval; NA, data not available.

monotherapy, until a gated blood pool scan indicated a decline in left ventricular ejection fraction (LVEF) from a baseline of 70 to 50%. Consequently, trastuzumab was permanently interrupted. Nevertheless, the CT scan performed two months later showed a complete response anyway. The patient remained disease-free for 6.5 years until the report was published.

Conversely, another case report demonstrated early relapse of a woman with HER2-positive MBC who experienced a complete remission for 2 years and had discontinued trastuzumab almost three years later (8). Two months after the withdrawal the patient had an episode of transient ischemic attack. The subsequent brain CT scan revealed multiple brain lesions with contrast enhancement. Therefore, she was scheduled for whole-brain radiation and restarted systemic therapy with trastuzumab plus weekly paclitaxel. The short period between drug interruption and relapse, however, was insufficient to determine whether recurrence may have been avoided or at least delayed. Since brain CT scan was not performed at regular intervals, cerebral metastases may have grown before trastuzumab was stopped.

Some institutional guidelines suggest at least 5 years of maintenance treatment with trastuzumab, although the effectiveness of this kind of approach has not been proven (24).

In a retrospective study, Gullo *et al* compared the long-term outcome of HER2-positive metastatic patients treated in Dublin, who continued on trastuzumab until progression or at least for five years, with that of patients treated in Milan, where trastuzumab was interrupted in CR-patients within two years of achieving remission (24). Albeit the percentage of patients who achieved a CR was very close in the two hospitals (Dublin 15% and Milan 16%), the Irish population showed a higher rate of patients with a durable complete response (DCR) (11 vs. 6% respectively), encouraging hypotheses regarding the optimal duration of trastuzumab.

Our patient received several treatments prior to reaching a complete response after 22 months since the start: she began with anthracyclines and taxanes, continued with Letrozole and Trastuzumab and then underwent surgery. Each treatment may have played a contributory role to the achievement of a complete response. Unquestionably, continuation of trastuzumab plus hormonal therapy led to the patient remaining disease-free for almost 10 years.

The role of Pertuzumab. At the time the patient began treatment, Pertuzumab was not available yet. Subsequently, only Trastuzumab was administered achieving a durable response anyway. The report underlines that some HER2+ MBC patients may benefit for a long time from Trastuzumab alone as first-line anti-HER2 target therapy; this means that the use of doublet with Pertuzumab plus Trastuzumab as first-line anti-HER2 targeted therapy should be unnecessary in some selected HER2+ MBC patients who have a good prognosis just with trastuzumab alone (plus endocrine therapy in HR+ breast cancers). On this basis, the subgroup analysis of the CLEOPATRA trial (25) revealed that patients with HR-positive and especially the ones with non-visceral disease seemed to benefit less from pertuzumab administration. The reported hazard ratio for these two groups were 0.73 (95% CI: 0.58-0.91) and 0.83 (95%: 0.58-1.18) respectively, compared with an HR of 0.64 (95% CI: 0.51-0.81) in HR-negative breast cancers and of 0.64 (95%: 0.53-0.76) in patients with visceral disease. The association between visceral involvement and outcome in pertuzumab-treated patients was even stronger in terms of OS (P=0.03), as reported by the prespecified overall survival analysis with a median follow-up of 50 months.

To conclude, a deeper analysis of clinical and molecular characteristics of long responders is required in order to identify patients who may benefit from durable HER-2 suppression. In particular, to clarify the role of Pertuzumab in this setting becomes crucial looking also at economic sustainability of oncological drugs. Although further research is underway, at present available evidences appear to foster continuous use of anti-HER2 therapies until disease progression.

References

1. Del Mastro L, Lambertini M, Bighin C, Levaggi A, D'Alonzo A, Giraudi S and Pronzato P: Trastuzumab as first-line therapy in HER2-positive metastatic breast cancer patients. Expert Rev Anticancer Ther 12: 1391-1405, 2012.
2. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, *et al*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344: 783-792, 2001.
3. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Knott A, *et al*: Overall survival benefit with pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer in CLEOPATRA, a randomised Phase 3 study. Lancet Oncol 14: 461-471, 2013.
4. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, *et al*: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366: 109-119, 2012.
5. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, van de Wouw AJ, Peters FP, van Riel JM, Peters NA, *et al*: Prognosis of metastatic breast cancer subtypes: The hormone receptor/HER2-positive subtype is associated with the most favorable outcome. Breast Cancer Res Treat 141: 507-514, 2013.
6. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Knott A, *et al*: Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 14: 461-471, 2013.
7. Maciá Escalante S, Rodríguez Lescure A, Pons Sanz V, Martínez Banaclocha N, Guillén Ponce C and Carrato Mena A: A patient with breast cancer with hepatic metastases and a complete response to herceptin as monotherapy. Clin Transl Oncol 8: 761-763, 2006.
8. Beda M, Basso U, Ghiotto C and Monfardini S: When should trastuzumab be stopped after achieving complete response in HER2-positive metastatic breast cancer patients? Tumori 93: 491-492, 2007.
9. Badulescu F, Badulescu A, Paul D, Popescu CF and Florescu C: More than 9 years of continuous trastuzumab treatment in metastatic breast cancer without cardiac toxicity: A case report and literature review. Onco Targets Ther 7: 1911-1917, 2014.
10. Artac M, Koral L, Toy H, Guler T, Boruban MC and Altundag K: Complete response and long-term remission to anti-HER2 combined therapy in a patient with breast cancer presented with bone marrow metastases. J Oncol Pharm Pract 20: 141-145, 2014.
11. Ihnenfeld Arciénega I, Imesch P, Fink D and Dedes KJ: Prolonged complete remission of metastatic HER2-positive breast cancer after continuous trastuzumab treatment: A case report and review of the literature. Target Oncol 10: 297-301, 2015.
12. Syrios J, Dokou A and Tsavaris N: Sustained complete remission of human epidermal growth factor receptor 2-positive metastatic breast cancer in the liver during long-term trastuzumab (Herceptin) maintenance therapy in a woman: A case report. J Med Case Rep 4: 401, 2010.

13. Hsieh A, Pittman K, Patterson WK and Townsend A: Can maintenance trastuzumab be stopped in patients with HER2-positive metastatic breast cancer? BMJ Case Rep 2015: pii: bcr2014207750, 2015.
14. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S and Senkus E; ESMO Guidelines Working Group: Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23 (Suppl 7): vii11-vii19, 2012.
15. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, *et al*: Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American society of clinical oncology clinical practice guideline. J Clin Oncol 32: 2078-2099, 2014.
16. Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, *et al*: III ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol Feb 19, 2017 (Epub ahead of print).
17. Yeo B, Kotsori K, Mohammed K, Walsh G and Smith IE: Long-term outcome of HER2 positive metastatic breast cancer patients treated with first-line trastuzumab. Breast 24: 751-757, 2015.
18. Witzel I, Müller V, Abenhardt W, Kaufmann M, Schoenegg W, Schneeweis A and Jänicke F: Long-term tumor remission under trastuzumab treatment for HER2 positive metastatic breast cancer-results from the HER-OS patient registry. BMC Cancer 14: 806, 2014.
19. Luen SJ, Salgado R, Fox S, Savas P, Eng-Wong J, Clark E, Kiermaier A, Swain SM, Baselga J, Michiels S and Loi S: Tumour-infiltrating lymphocytes in advanced HER2-positive breast cancer treated with pertuzumab or placebo in addition to trastuzumab and docetaxel: A retrospective analysis of the CLEOPATRA study. Lancet Oncol 18: 52-62, 2017.
20. Yardley DA, Tripathy D, Brufsky AM, Rugo HS, Kaufman PA, Mayer M, Magidson J, Yoo B, Quah C and Ulcickas Yood M: Long-term survivor characteristics in HER2-positive metastatic breast cancer from registHER. Br J Cancer 110: 2756-2764, 2014.
21. Harano K, Lei X, Gonzalez-Angulo AM, Murthy RK, Valero V, Mittendorf EA, Ueno NT, Hortobagyi GN and Chavez-MacGregor M: Clinicopathological and surgical factors associated with long-term survival in patients with HER2-positive metastatic breast cancer. Breast Cancer Res Treat 159: 367-374, 2016.
22. Fiteni F, Villanueva C, Bazan F, Perrin S, Chaigneau L, Dobi E, Montcuquet P, Cals L, Meneveau N, Nerich V, *et al*: Long-term follow-up of patients with metastatic breast cancer treated by trastuzumab: Impact of institutions. Breast 23: 165-169, 2014.
23. Murthy P, Kidwell KM, Schott AF, Merajver SD, Griggs JJ, Smerage JD, Van Poznak CH, Wicha MS, Hayes DF and Henry NL: Clinical predictors of long-term survival in HER2-positive metastatic breast cancer. Breast Cancer Res Treat 155: 589-595, 2016.
24. Gullo G, Zuradelli M, Sclafani F, Santoro A and Crown J: Durable complete response following chemotherapy and trastuzumab for metastatic HER2-positive breast cancer. Ann Oncol 23: 2204-2205, 2012.
25. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, *et al*: Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 372: 724-734, 2015.