

CASE REPORT

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# Complete pathologic response of HER2-positive breast cancer liver metastasis with dual Anti-HER2 antagonism

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## Abstract

**Background:** Although breast cancer frequently metastasizes to the bones and brain, rarely breast cancer patients may develop isolated liver metastasis. There is increasing data that anti-HER2 targeted therapy in conjunction with systemic chemotherapy may lead to increased rates of pathologic complete response in the primary breast cancer. However, little is known about its effects on metastatic liver disease.

**Case presentation:** We report the treatment of a 54-year-old female who was diagnosed with HER2-positive invasive ductal carcinoma and synchronous breast cancer liver metastasis (BCLM). The patient underwent eight cycles of standard docetaxel with two anti-HER2 targeted agents, trastuzumab and pertuzumab. Subsequent radiographic imaging demonstrated complete radiographic response in the primary lesion with an approximate 75% decrease in the liver metastasis. After informed consent the patient underwent modified radical mastectomy that revealed pathologic complete response. Re-staging demonstrated no new disease outside the liver and a left hepatectomy was performed for resection of BCLM. Final pathologic examination revealed no residual malignant cells in the liver specimen, indicating pathologic complete response. Herein, we discuss the anti-HER2 targeted agents trastuzumab and pertuzumab and review the data on dual HER2 antagonism for HER2-positive breast cancer and the role of surgical resection of BCLM.

**Conclusions:** The role of targeted agents for metastatic HER2-positive breast cancer is under active clinical trial investigation and we await the maturation of trial results and long-term survival data. Our results suggest that these agents may also be effective for producing considerable pathologic response in patients with BCLM.

**Keywords:** HER2-positive breast cancer, Targeted therapy, Breast cancer liver metastases, Trastuzumab, Pertuzumab, Complete pathologic response

## Background

Breast cancer is a major public health concern and affects tens of thousands of women worldwide each year. In approximately 25% of patients, the breast cancer cells over-express human epidermal growth factor receptor-2 (HER2) on the cell surface, which results in a more aggressive breast cancer phenotype and significantly decreased overall and disease-specific survival compared with patients whose breast cancer does not overexpress HER2 [1]. Monoclonal antibodies, such as trastuzumab, that bind to HER2 proteins can be used along with chemotherapy to

treat patients with HER2-overexpressing breast cancer with metastases to organs outside of the breast. In this paper we present a case of HER2-positive breast cancer liver metastasis successfully treated with anti-HER2 targeted therapy resulting in a complete pathologic response.

## Case presentation

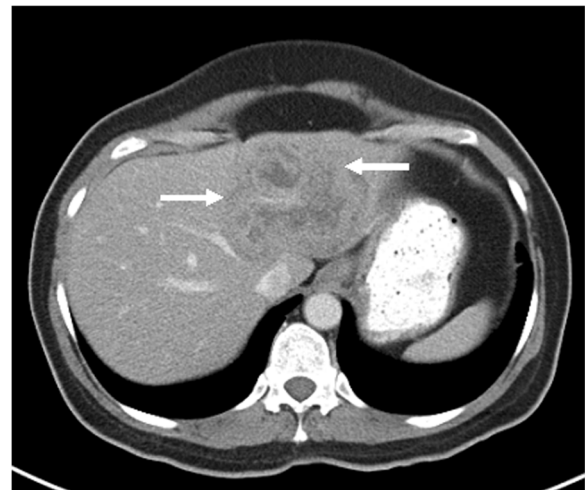
A 54-year-old Caucasian female with no past medical history or co-morbidities presented to an outside institution with 3-month history of an enlarging palpable mass in her left breast associated with skin thickening and nipple retraction. The patient reported rapid growth of the mass over the preceding month. Mammography was ordered and revealed a 10 × 4 × 6 cm mass in the upper outer quadrant of the left breast associated with pleomorphic calcifications (Figure 1). Ultrasound-guided biopsy

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**Figure 1** Medial-lateral oblique mammogram of the left breast demonstrating a large spiculated mass with calcifications in the upper aspect of the breast (marked by arrows); biopsy of the mass revealed HER2-overexpressing infiltrating ductal breast cancer.



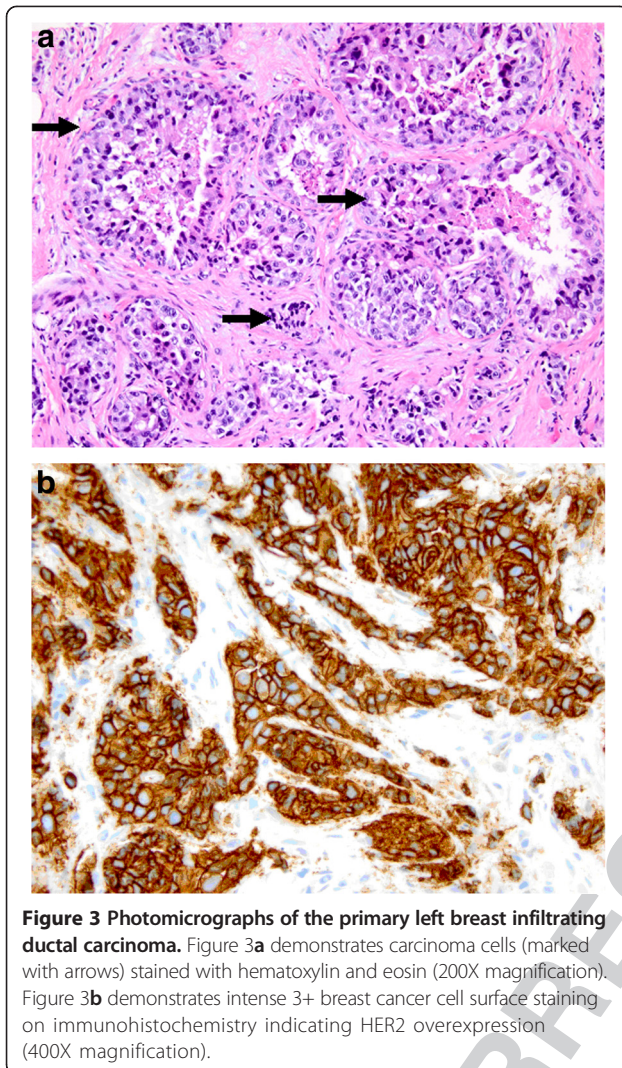
**Figure 2** Pre-treatment CT scan of the abdomen showing a large hypodense mass in the left lobe of the liver (marked by arrows); biopsy of the mass revealed metastatic HER2-positive breast cancer.

55 of this ill-defined hypoechoic mass demonstrated poorly-  
56 differentiated, grade 3 of 3, ER-negative, PR-negative,  
57 HER2-positive infiltrating ductal carcinoma. Biopsy of an  
58 enlarged 1.4 cm left axillary lymph node revealed meta-  
59 static adenocarcinoma. Human epidermal growth factor  
60 receptor-2 (HER2) protein expression was 3+ by immuno-  
61 histochemistry and HER2 gene was amplified with a ratio  
62 of 6.7 by fluorescence in situ hybridization; Ki-67 was  
63 markedly elevated at 50%. High-grade comedo and solid  
64 ductal carcinoma in situ (DCIS) was also identified. Meta-  
65 static workup with computed tomographic scans of the  
66 chest, abdomen, and pelvis revealed an 8.2 × 6.8 cm mass  
F2 67 in the left lobe of the liver (Figure 2), but no evidence of  
68 metastatic disease elsewhere. The liver lesion was biopsied  
69 and showed adenocarcinoma that was ER/PR-negative and  
F3 70 HER2-positive (Figure 3a and 3b), consistent with meta-  
71 static breast cancer.

Given the HER2-positive status, the patient was sched- 72  
uled to receive chemotherapy in combination with HER2- 73  
targeted monoclonal antibody trastuzumab, which binds 74  
to HER2 and disrupts cell signaling and proliferation 75  
[1]. Prior to the initiation of therapy, the US Food and 76  
Drug Administration approved another anti-HER2 targeted 77  
monoclonal antibody, pertuzumab, for first-line treatment 78  
of HER2-positive metastatic breast cancer in combination 79  
with docetaxel and trastuzumab. The approval was based 80  
on results from the randomized Phase III Clinical Evalu- 81  
ation of Pertuzumab and Trastuzumab (CLEOPATRA) trial 82  
which showed increased progression-free survival (PFS) in 83  
HER2-positive metastatic breast cancer patients treated 84  
with docetaxel, trastuzumab, and pertuzumab compared to 85  
docetaxel and trastuzumab alone. 86

The patient underwent eight cycles of docetaxel (75 mg/ 87  
m<sup>2</sup> every three weeks), trastuzumab (8 mg/kg loading dose 88  
on Day 2 of the first cycle followed by 6 mg/kg every three 89  
weeks thereafter), and pertuzumab (840 mg loading dose 90  
on Day 2 of the first cycle followed by 420 mg every three 91  
weeks thereafter) over a total period of six months. The 92  
patient tolerated therapy without adverse effects and 93  
underwent re-staging with PET/CT after the 4th cycle 94  
of treatment, demonstrating near 75% reduction in the 95  
breast lesion. Additionally, the liver metastasis decreased 96  
in size from 8 cm to 5 cm. Re-staging imaging studies 97  
after the 8th cycle of therapy showed radiographic resolu- 98  
tion of the left breast mass and interval decrease of the 99  
liver mass to 2 cm. 100

Since retrospective studies have suggested improved 101  
survival for patients with stage IV breast cancer with re- 102  
section of the primary tumor [2,3] and given the patient's 103  
remarkable therapeutic response, consideration was given 104



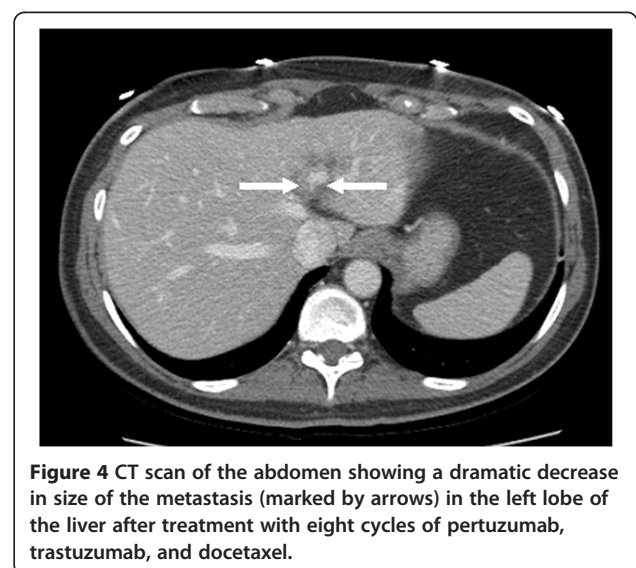
hepatic lobe metastasis to be 2.3 × 2 cm without evidence of metastatic disease elsewhere (Figure 4). The liver lesion was deemed to be resectable and the patient underwent left hepatectomy approximately five months after modified radical mastectomy had been performed. The patient's post-operative course was uncomplicated and she was subsequently discharged home in excellent condition. Final pathologic examination of the resected specimen revealed an area of scar tissue with stromal hyalinization, scattered histiocytes, and lymphocytic infiltrate measuring 1.2 cm. No residual malignant cells were identified in the resected liver, thus indicating a complete pathologic response (Figure 5). On surveillance imaging approximately three months after resection, repeat CT of the abdomen/pelvis demonstrated no evidence of new or recurrent disease in the liver (Figure 6). The patient continues to do well without disease approximately 6 months after liver surgery. Currently the optimal duration of anti-HER2 therapy for patients with long-term disease control is not known [4], and as such the patient will remain on dual agent pertuzumab and trastuzumab given every three weeks indefinitely.

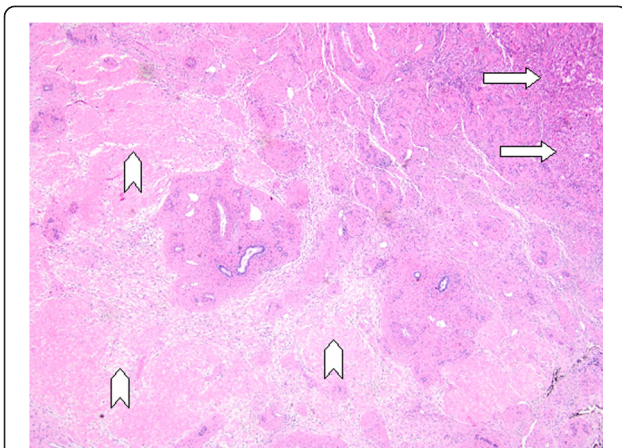
### Discussion

Breast cancer is the most common cancer in women worldwide, accounting for 1.3 million new cases in 2008 (23% of all new cases) [5]. Ten to 15% of patients have metastatic disease at the time of initial presentation [6], and the most common sites of metastases are the bones and brain with only 1-5% of breast cancer patients developing isolated liver metastasis [7,8]. Aggressive tumor biology and corresponding poorer prognosis is associated with amplification or overexpression of HER2, a transmembrane tyrosine kinase protein belonging to the human

to resection of the primary breast cancer following the 8th treatment cycle. As such, the patient underwent left modified radical mastectomy with tissue-expander reconstruction seven months after the diagnosis of stage IV breast cancer was made. Final pathologic examination revealed residual high-grade DCIS with necrosis (2.7 cm); however no residual invasive carcinoma was identified. Therefore, pathologic complete response (i.e., ypTisN0M1) of the invasive tumor was observed. Due to the original size of the primary lesion, the patient received standard post-mastectomy radiation therapy to the left chest wall and nodal basin. After the breast operation the patient was continued on trastuzumab 6 mg/kg and pertuzumab 420 mg given every three weeks.

The patient subsequently transferred her care to our institution and was evaluated for resection of the liver metastasis. Triple-phase CT scan at our institution taken 12 months after her initial presentation revealed the left





**Figure 5** Photomicrograph of the left hepatectomy specimen stained with hematoxylin and eosin, demonstrating normal liver parenchyma marked with arrows, fibrotic tissue with hyalinization and scattered lymphocytic infiltrate (marked by arrowheads) without evidence of breast cancer cells, consistent with response to treatment and indicating complete pathologic response (40X magnification).

156 epidermal growth factor receptor (EGFR) family of pro-  
157 teins [9]. Historically, patients with HER2-positive breast  
158 cancer have had poor prognosis, with response rates to  
159 chemotherapy ranging from 17-42% [1]. Now with the ad-  
160 vent of anti-HER2 therapy, tumor response and patient  
161 survival have dramatically improved [10,11].

162 The first anti-HER2 targeted agent was the monoclonal  
163 antibody trastuzumab, which initially was approved for  
164 the treatment of HER2-overexpressing breast cancer with  
165 standard chemotherapy in the metastatic setting. Trastu-  
166 zumab inhibits ligand-independent HER2 activity and re-  
167 lated downstream signaling by binding to its extracellular



**Figure 6** CT scan of the abdomen performed three months after resection of the left lobe of the liver demonstrating normal-appearing right lobe of the liver without evidence of new or recurrent metastatic disease.

domain [12,13]; however trastuzumab binding does not  
169 interfere with HER2 heterodimerization, which mediates  
170 downstream cell proliferation [14]. Pertuzumab, the sec-  
171 ond commercially approved selective anti-HER2 agent,  
172 may act in synergy with trastuzumab to antagonize HER2  
173 signaling by blocking HER2 heterodimerization and acti-  
174 vating antibody-dependent cell-mediated cytotoxicity [15].

Treatment of HER2-positive breast cancer patients with  
175 dual anti-HER2 antagonism translates to better thera-  
176 peutic responses. In the CLEOPATRA trial approximately  
177 80% of patients randomized to the experimental treatment  
178 (docetaxel, trastuzumab, and pertuzumab) had an objec-  
179 tive tumor response compared to 69.3% with control treat-  
180 ment (docetaxel and trastuzumab) [13]. In a Phase II trial  
181 by Baselga *et al.*, patients with metastatic HER2-positive  
182 breast cancer received trastuzumab with pertuzumab and  
183 had response rates of 24.2%, and 7.6% of patients had a  
184 pathologic complete response [16]. In another Phase II  
185 trial, the Neoadjuvant Study of Pertuzumab and Herceptin  
186 in an Early Regimen Evaluation (NeoSphere) Trial, the  
187 highest rates of pathologic complete response were ob-  
188 served in patients receiving docetaxel, trastuzumab, and  
189 pertuzumab. Interestingly, in patients receiving targeted  
190 therapy alone (i.e., trastuzumab and pertuzumab) approxi-  
191 mately 17% of patients had pathologic complete response,  
192 demonstrating that dual HER2 inhibition alone may elicit  
193 remarkable responses in HER2-positive breast cancers  
194 [17]. Unfortunately, none of the aforementioned trials spe-  
195 cifically characterize metastatic liver disease and it is un-  
196 clear whether such results could reasonably be applied to  
197 any metastatic site.

Our experience indicates that HER2-overexpressing  
199 BCLM can be effectively treated with chemotherapy and  
200 dual HER2 targeted therapy. This is important for pa-  
201 tients with isolated liver metastases (1-5% of all meta-  
202 static patients), because control and possibly cure of the  
203 disease can be achieved. Indeed, liver resection has become  
204 a treatment option for selected patients with BCLM. Prior  
205 to the modern era, older studies showed no survival advan-  
206 tage for metastatic breast cancer patients who underwent  
207 liver resection, with five-year survival of 9% seen [18-20].  
208 Now, contemporary studies routinely report survival advan-  
209 tages in select patients undergoing liver resection for  
210 BCLM. Five-year overall survival rates approaching 21%-  
211 38% are the norm with a combination of chemotherapy  
212 and resection, and a wide variety of chemotherapeutic re-  
213 gimens have been reported to be used in the literature,  
214 commonly Adriamycin/cyclophosphamide or cyclophos-  
215 phamide/methotrexate/fluorouracil [7,8,21]. The survival  
216 rate of breast cancer patients with isolated liver metastasis  
217 who have undergone liver resection has dramatically in-  
218 creased due to medical advances and multidisciplinary  
219 care: improved chemotherapy and targeted agents, more  
220 effective surgery and better post-operative care. For  
221

222 patients with HER2-positive BCLM, we expect that out-  
223 comes in the future will be even further improved given  
224 the high rates of tumor response to HER2 targeted ther-  
225 apy and the possibility of achieving a complete pathologic  
226 response.

## 227 Conclusion

228 The role of HER2 targeted agents such as pertuzumab will  
229 continue to evolve in the treatment of patients with  
230 BCLM, and may lead to curative therapeutic plans. There  
231 is no data on pathologic complete response from this new  
232 treatment option and we anticipate that our experience  
233 may prove in the future to be a common and frequent  
234 outcome. Targeted agents in combination with chemo-  
235 therapy will undoubtedly increase the resectability of liver  
236 metastasis. Continued multi-disciplinary treatment strat-  
237 egies will be essential in the future to coordinate the roles  
238 of targeted therapy and liver resection, ultimately with the  
239 goal of providing patients improved survival benefit.

## 240 Consent

241 Written informed consent was obtained from the patient  
242 for publication of this Case Report and any accompanying  
243 images. A copy of the written consent is available for re-  
244 view by the Editor of this journal.

## 245 Competing interests

246 The authors declare that they have no competing interests.

## 247 Authors' contributions

248 HFS obtained the radiographic and pathologic images and drafted the  
249 manuscript. FH and CV helped to draft the manuscript. PC read the  
250 pathologic slides, captured the images, and helped draft the manuscript. JP  
251 read the radiographic images and helped draft the manuscript. JW helped  
252 draft the manuscript. JK conceived of the case report, participated in its  
253 design and coordination, and helped draft the manuscript. All authors read  
254 and approved the final manuscript.

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