Prognostic Factors in HER2-Positive Primary Breast Cancer Patients Treated Using Neoadjuvant Chemotherapy Plus Trastuzumab

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Keywords

Breast cancer · Human epidermal growth factor receptor 2 · Neoadjuvant chemotherapy · Prognostic factors · Trastuzumab

Abstract

Background: It is unclear for whom new anti-human epidermal growth factor receptor 2 (anti-HER2) agents, such as pertuzumab and T-DM1, should be considered. We investigated prognostic factors before neoadjuvant chemotherapy (NAC) among HER2-positive invasive breast cancer patients and those after NAC among patients who did not achieve pathological complete response (pCR) using conventional adjuvant trastuzumab. **Methods:** HER2-positive primary breast cancer patients treated using NAC containing trastuzumab were enrolled between September 2006 and June 2017 at the Osaka Breast Clinic. Patients with distant metastasis or using NAC containing pertuzumab were excluded. The main outcome was disease-free survival (DFS). We investigated pre- and post-NAC prognostic factors using the log-rank test and Cox proportional hazards model. **Results:** In total, 157 patients were included. Among the pre-NAC prognostic fac-

tors, younger age (under 40 years old) and positive clinical nodal status were significantly poorer prognostic factors (hazard ratio [HR] 3.47, 95% CI 1.06–10.12, $p = 0.041$ and HR 3.32, 95% CI 1.03–14.78, $p = 0.045$) by multivariate analysis. Among the post-NAC prognostic factors, patients with non-pCR (3-year DFS; 85 vs. 96%, $p = 0.022$) had a poorer DFS than patients with pCR. DFS was assessed for non-pCR patients ($n = 64$). High post-NAC Ki-67 status ($\geq 20\%$; HR 6.73, 95% CI 1.82–31.93, $p = 0.004$) was a significant and large post-NAC tumor size (≥ 2 cm; HR 3.65, 95% CI 0.97–14.71, $p = 0.056$) was a marginally significant prognostic factor by multivariate analysis. After having combined them, high post-NAC Ki-67 status or large post-NAC tumor size was also a significant prognostic factor (HR 5.75, 95% CI 1.32–16.12, $p = 0.017$). **Conclusions:** Positive clinical nodal status and young age were found to be prognostic factors before NAC in HER2-positive invasive breast cancer patients. A high post-NAC Ki-67 status and large post-NAC tumor size were significant and marginally significant prognostic factors, respectively, after NAC in patients who did not achieve pCR. New anti-HER2 agents, such as pertuzumab and T-DM1, should be considered for the patients with those prognostic factors.

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Introduction

Human epidermal growth factor receptor 2 (HER2) overexpression in breast cancer is associated with a poorer prognosis [1]. Neoadjuvant and adjuvant chemotherapy with trastuzumab significantly improve the prognosis of patients with HER2-positive breast cancer [2, 3], but some patients still have a poor prognosis.

Pertuzumab increases the rates of pathological complete response (pCR) and overall survival (OS) among patients with metastatic disease when it is added to trastuzumab and chemotherapy for the treatment of HER2-positive advanced breast cancer [4, 5]. Moreover, it significantly improves the invasive disease-free survival (DFS) rate among patients with HER2-positive operable breast cancer when added to trastuzumab and chemotherapy [6]. Therefore, pertuzumab was recently approved for HER2-positive primary breast cancer, but it is unclear who should receive it [7]. There is little evidence in the neoadjuvant setting and pertuzumab is expensive. Thus, prognostic information before neoadjuvant chemotherapy (NAC) is important when deciding whether pertuzumab should be added to trastuzumab and chemotherapy.

Trastuzumab emtansine (T-DM1) was recently reported to significantly improve the invasive DFS rate among patients with HER2-positive early breast cancer who had residual invasive disease after NAC [8]. T-DM1 will be approved for patients with HER2-positive early breast cancer who had residual invasive disease after NAC, but there will be more adverse events with T-DM1 than with adjuvant trastuzumab and T-DM1 is more expensive than trastuzumab. Among patients who did not achieve pCR, there will still be those who have a good prognosis using adjuvant trastuzumab without pertuzumab or T-DM1. As such, it is important to identify prognostic factors in patients with non-pCR and T-DM1 should be administered to those who have a poorer prognosis.

This study investigated prognostic factors before NAC among HER2-positive invasive breast cancer patients and those after NAC among patients who did not achieve pCR using conventional adjuvant trastuzumab.

Materials and Methods

Patients

HER2-positive primary breast cancer patients treated using NAC were enrolled between September 2006 and June 2017 at the Osaka Breast Clinic. The inclusion criteria were female sex, histo-

logically confirmed HER2-positive invasive breast cancer, no distant metastasis, and NAC treatment containing trastuzumab. Patients with advanced breast cancer treated using NAC containing pertuzumab were excluded.

Treatment

NAC is mainly composed of taxane-based regimens followed by anthracycline-based regimens: 12 cycles of paclitaxel (80 mg/m² every week) or 4 cycles of docetaxel (75 mg/m² every 3 weeks); and 4 cycles of FEC (fluorouracil at 500 mg/m², epirubicin at 100 mg/m², and cyclophosphamide at 500 mg/m² every 3 weeks). A small proportion of patients received other taxane-based regimens. All patients received trastuzumab regimens (8 mg/kg as a loading dose and 6 mg/kg from the second dose onward every 3 weeks) concurrently with a taxane-based regimen. Surgery was performed 5–6 weeks after the final dose of the NAC. After surgery, all patients received adjuvant trastuzumab. Patients received a total of 18 doses of trastuzumab. Patients with estrogen receptor (ER)-positive tumors were scheduled to receive adjuvant endocrine therapy for 5–10 years.

Pathological Assessment

ER, progesterone receptor (PgR), HER2 status, and Ki-67 status were evaluated by core needle biopsy before NAC by immunohistochemistry. The Ki-67 status was also evaluated in residual tumors after NAC by immunohistochemistry. The cutoff values for ER, PgR, and Ki-67 were 10, 10, and 20%, respectively. HER2-positive status was defined as 3+ overexpression by immunohistochemical testing or HER2 amplification by fluorescence in situ hybridization (HER2/CEP17 ratio ≥ 2.0) based on the ASCO CAP criteria [9]. Thirty-one patients who were diagnosed at other institutions at an early time did not obtain pre-NAC Ki-67 status. Post-NAC Ki-67 status of all tissues from operation were evaluated at our institution, but 8 cases were difficult to evaluate because of a chemotherapy effect. Pathological response to chemotherapy was evaluated by examining the surgical specimens obtained during surgery. pCR was defined as the absence of residual invasive cancer cells in the breast and axillary lymph nodes (ypT0/is + ypN0) [10].

Statistical Analysis

All survival outcomes were measured from the date of starting NAC to the date of recurrence of breast cancer (local or distant) or death of any cause. DFS and OS were assessed using the Kaplan-Meier method and log-rank tests, and univariate and multivariate analyses (Cox regression models) were used to evaluate the prognostic significance of different parameters. Multivariate analyses included the parameters $p < 0.1$ and a conventional prognostic factor with $p < 0.3$. All statistical analyses were performed using JMP (version 10).

Results

Patient Characteristics

Baseline characteristics and treatments are summarized in Table 1. In total, 157 patients were included. The median age was 51 years (range 24–72). The clinical staging was as follows: cStage I, 27 patients; cStage IIA, 58

patients; cStage IIB, 41 patients; cStage IIIA, 14 patients; cStage IIIB, 6 patients; and cStage IIIC, 11 patients. Most patients had tumor stage T2 (63.1%) and positive clinical nodal status (51.6%). ER and PgR were negative in 55.4% of the patients. Most patients received anthracycline- and taxane-containing chemotherapy (80.9%; Table 1).

Clinical Outcomes

The median follow-up period was 44 months (range 10–150). For all patients, the 3-year DFS and OS rates were 91 and 97%, respectively (Fig. 1a, b).

Prognostic Factors before NAC

Among the pre-NAC prognostic factors, younger patients (under 40 years old) had a significantly poorer DFS (3-year DFS; 84 vs. 93%; $p = 0.048$) than older patients, whereas those with a positive clinical nodal status had a marginally poorer DFS (87 vs. 96%, $p = 0.068$; Fig. 2a, b). Univariate and multivariate analyses were next conducted. By multivariate analysis, younger age was significantly associated with a poorer DFS (hazard ratio [HR] 3.47, 95% CI 1.06–10.12, $p = 0.041$), as was positive clinical nodal status (HR 3.32, 95% CI 1.03–14.78, $p = 0.045$; Table 2). We excluded pre-NAC Ki status from analysis because there were some missing values.

Prognostic Factors after NAC among Patients Who Did Not Achieve pCR

Among the post-NAC prognostic factors, patients with non-pCR (3-year DFS; 85 vs. 96%, $p = 0.022$) had a poorer DFS than patients with pCR (Fig. 3). In the 64 non-pCR patients, patients with a large post-NAC tumor size (≥ 2 cm) had a significantly poorer DFS than patients without these factors (72 vs. 91%, $p = 0.0246$) and patients with a high post-NAC Ki-67 status ($\geq 20\%$) also had a significantly poorer DFS (56 vs. 94%, $p = 0.0012$; Fig. 4a, b). After combining the post-NAC Ki-67 status and post-NAC tumor size, patients with a small post-NAC tumor size and low post-NAC Ki-67 status ($n = 34$) had a better prognosis than the others ($n = 30$; 97 vs. 72%, $p = 0.004$; Fig. 4c). Univariate and multivariate analyses were next conducted. By univariate analysis, a high post-NAC Ki-67 status ($\geq 20\%$; HR 6.86, 95% CI 1.90–31.90, $p = 0.003$), large post-NAC tumor size (≥ 2 cm; HR 3.83, 95% CI 1.09–14.99, $p = 0.036$) and positive post-NAC lymph node status (ypN1; HR 4.67, 95% CI 1.30–21.68, $p = 0.018$) were prognostic factors. By multivariate analysis, a high post-NAC Ki-67 status ($\geq 20\%$; HR 6.73, 95% CI 1.82–31.93, $p = 0.004$) was an independent and a large post-NAC tumor size (≥ 2 cm) was a marginally signifi-

Table 1. Patient, disease and treatment characteristics

All breast carcinomas	157 (100.0)
pre-NAC factors	
Age, years median (range)	51 (24–72)
Age	
<40 years	25 (15.9)
≥ 40 years	132 (84.1)
Clinical T stage	
T1	39 (24.8)
T2	99 (63.1)
T3	10 (6.4)
T4	9 (5.7)
Clinical tumor size	
≤ 3 cm	91 (58.0)
> 3 cm	66 (42.0)
Clinical nodal status	
N0	76 (48.4)
$N \geq 1$	81 (51.6)
Histological/nuclear grade	
G1	13 (8.3)
G2	68 (43.3)
G3	60 (38.2)
Unknown	16 (10.2)
ER/PgR status	
Negative	87 (55.4)
Positive	70 (44.6)
Ki-67 status	
$\geq 20\%$	114 (72.6)
$< 20\%$	12 (7.6)
Unknown	31 (19.7)
NAC regimen	
Anthracycline and taxane	127 (80.9)
Taxane only	30 (19.1)
pCR (ypT0/is + ypN0)	
None	64 (40.8)
Yes	93 (59.2)
Reduction rate	
$< 30\%$ (SD, PD)	15 (9.6)
$\geq 30\%$ (PR, CR)	136 (86.6)
Unknown	6 (3.8)
Non pCR	64 (100.0)
Post-NAC tumor size	
≤ 2 cm	46 (71.8)
> 2 cm	18 (28.1)
Post-NAC Ki-67 status	
$\geq 20\%$	17 (26.6)
$< 20\%$	39 (60.9)
Unknown	8 (12.5)
Post-NAC lymph node status	
N0 (ypN0)	42 (65.6)
$N \geq 1$ (ypN1)	22 (34.4)

Figures are n (%) unless where indicated otherwise.

Fig. 1. Disease-free survival (a) and overall survival (b) curves of all patients.

Fig. 2. Disease-free survival in relation to age (a) and clinical node status (b).

Fig. 3. Disease-free survival in relation to pathological response.

cant prognostic factor (HR 3.65, 95% CI 0.97–14.71, $p = 0.056$). After having combined post-NAC Ki-67 status and post-NAC tumor size, high post-NAC Ki-67 status or large post-NAC tumor size was also a significant prognostic factor by both univariate (HR 7.18, 95% CI 2.59–21.43, $p < 0.001$) and multivariate analysis (HR 5.75, 95% CI 1.32–16.12, $p = 0.017$; Table 3).

Discussion

In the present study, we assessed prognostic factors before NAC among HER2-positive invasive breast cancer patients and those after NAC among patients who did not achieve pCR using conventional adjuvant trastuzumab.

Fig. 4. Prognosis of NAC-treated breast cancer patients without pCR ($n = 64$). Disease-free survival in relation to post NAC- Ki-67 status (**a**), post-NAC tumor size (**b**) and combination of post-NAC Ki-67 status and post-NAC tumor size (**c**). pCR, pathological complete response.

Table 2. Univariate and multivariate analysis of various prognostic factors before NAC for disease-free survival

Factors	Total patients ($n = 157$)					
	univariate analysis			multivariate analysis		
	hazard ratio	95% CI	p value	hazard ratio	95% CI	p value
Age, years (< 40 vs. ≥ 40)	2.83	0.88–7.97	0.078	3.47	1.06–10.12	0.041
Clinical T stage (T2,3,4 vs. T1)	1.78	0.49–11.44	0.418			
Clinical T stage (T3,4 vs. T1,2)	1.60	0.36–5.08	0.491			
Clinical tumor size (> 3 vs. ≤ 3 cm)	1.75	0.62–5.25	0.289	1.77	0.63–5.40	0.281
Clinical nodal status ($N \geq 1$ vs. N0)	3.09	0.97–13.68	0.057	3.32	1.03–14.78	0.045
Histological/nuclear grade (3 vs. 1,2)	0.66	0.18–2.09	0.486			
ER/PgR status (positive vs. negative)	1.72	0.61–5.52	0.312			

Among the pre-NAC prognostic factors, multivariate analysis demonstrated clinical N stage and younger age to be independent prognostic factors. Younger age was found to be marginally prognostic in one Japanese report

[11] but not in other reports [12]. One explanation is that Japanese people often develop breast cancer at a younger age than those in other countries [13, 14], and another explanation is that Japanese people have a longer life expect-

Table 3. Univariate and multivariate analysis of various prognostic factors after NAC for disease-free survival in non-pCR patients

Factors	Non-pCR patients (<i>n</i> = 64)								
	univariate analysis			multivariate analysis			multivariate analysis		
	hazard ratio	95% CI	<i>p</i> value	hazard ratio	95% CI	<i>p</i> value	hazard ratio	95% CI	<i>p</i> value
Reduction rate (<30 vs. ≥30%)	2.42	0.60–9.13	0.203						
Post-NAC lymph node status (ypN1 vs. ypN0)	4.67	1.30–21.68	0.018	2.11	0.71–13.32	0.147	2.45	0.73–8.49	0.145
Post-NAC tumor size (≥2 vs. <2 cm)	3.83	1.09–14.99	0.036	3.65	0.97–14.71	0.056			
Post-NAC Ki-67 status (≥20 vs. <20%)	6.86	1.90–31.90	0.003	6.73	1.82–31.93	0.004			
Combined post-NAC tumor size and post-NAC Ki-67 status ^a	7.18	2.59–21.43	<0.001				5.75	1.32–16.12	0.017

^a Post-NAC tumor size ≥2 cm or post-NAC Ki-67 status ≥20% vs. post-NAC tumor size <2 cm and post-NAC Ki67 status <20%.

tancy, with the average for Japanese women being 86 years old [15]. It is an important prognostic factor because young people have an important role in society, that is, parenting and labor. Pertuzumab as NAC should be added for younger patients or patients with a positive clinical nodal status because they have a poorer prognosis.

On assessment of the post-NAC factors after removing the patients who achieved pCR, a high post-NAC Ki-67 status was prognostic and a large post-NAC tumor size was marginally prognostic. Our results are consistent with those of several other studies reporting that a high post-NAC Ki-67 status is associated with a poor DFS [16–20]. A high Ki-67 status after NAC reflects high cell proliferation in the residual tumor and persistent aggressiveness regardless of strong chemotherapy; therefore, it significantly affects the DFS. This study demonstrated that the post-NAC Ki-67 status is important for HER2-positive breast cancer.

Our multivariate analysis revealed that a large post-NAC tumor size is a poorer prognostic factor than the reduction rate. Even if there is a large decrease in tumor size, if the post-NAC residual tumor size is large, the tumor is considered to have a high risk of recurrence.

We were able to identify patients with a better prognosis among non-pCR patients using the combination of post-NAC Ki-67 status and post-NAC tumor size. It is important to identify patients who do not need additional treatment because pertuzumab and T-DM1 are expensive, and not cost effective [21, 22].

The limitations of this study include its retrospective design. We identified prognostic factors in HER2-positive breast cancer patients treated using trastuzumab, but not predictive factors related to the effects of pertuzumab or T-DM1. The strength of our study was that all patients received NAC using adjuvant trastuzumab, thus the treat-

ment was specific. Moreover, we investigated prognostic factors among pre-NAC and post-NAC separately.

In conclusion, our study clarified prognostic factors before NAC among HER2-positive invasive breast cancer patients and those after NAC among patients who did not achieve pCR using conventional adjuvant trastuzumab. Positive clinical nodal status and young age were found to be prognostic among the pre-NAC factors, and a high post-NAC Ki-67 status and large post-NAC tumor size were significantly and marginally significantly prognostic, respectively, among the post-NAC factors. As older patients with a negative clinical nodal status, small post-NAC tumor size, and low post-NAC Ki-67 status have a good prognosis, traditional adjuvant trastuzumab may be sufficient. New anti-HER2 agents, such as pertuzumab and T-DM1, should be considered for other patients. Such an approach will benefit breast cancer patients with high-risk disease, although further studies, including a larger number of patients with a sufficient observation time, are needed.

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Statement of Ethics

This investigation was approved by the Institutional Review Board of Osaka Breast Clinic.

Disclosure Statement

The authors declare no conflict of interest.

References

- Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987 Jan;235(4785):177–82.
- Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017 Mar;389(10075):1195–205.
- Untch M, Fasching PA, Konecny GE, Hasmlüller S, Lebeau A, Kreienberg R, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol*. 2011 Sep;29(25):3351–7.
- Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015 Feb;372(8):724–34.
- Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012 Jan;13(1):25–32.
- von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017 Jul;377(2):122–31.
- Denduluri N, Somerfield MR, Giordano SH. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update Summary. *J Oncol Pract*. 2018 Aug;14(8):508–10.
- von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al.; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. 2019 Feb;380(7):617–28.
- Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al.; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013 Nov;31(31):3997–4013.
- von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012 May;30(15):1796–804.
- Takada M, Ishiguro H, Nagai S, Ohtani S, Kawabata H, Yanagita Y, et al. Survival of HER2-positive primary breast cancer patients treated by neoadjuvant chemotherapy plus trastuzumab: a multicenter retrospective observational study (JBCRG-C03 study). *Breast Cancer Res Treat*. 2014 May;145(1):143–53.
- Partridge AH, Gelber S, Piccart-Gebhart MJ, Focant F, Scullion M, Holmes E, et al. Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2-positive breast cancer: results from a herceptin adjuvant trial. *J Clin Oncol*. 2013 Jul;31(21):2692–8.
- Parkin DM, Ferlay J, Curado MP, Bray F, Edwards B, Shin HR, et al. Fifty years of cancer incidence: CI5 I-IX. *Int J Cancer*. 2010 Dec;127(12):2918–27.
- Kataoka A, Iwamoto T, Tokunaga E, Tomotaki A, Kumamaru H, Miyata H, et al. Young adult breast cancer patients have a poor prognosis independent of prognostic clinicopathological factors: a study from the Japanese Breast Cancer Registry. *Breast Cancer Res Treat*. 2016 Nov;160(1):163–72.
- Report of the Study Group for Japan's International Contribution to 'Active Aging' [Internet]. Available from: <https://www.mhlw.go.jp/file/05-Shingikai-10501000-Daijinkan-boukokusaika-Kokusaika/0000044929.pdf>.
- Tanei T, Shimomura A, Shimazu K, Nakayama T, Kim SJ, Iwamoto T, et al. Prognostic significance of Ki67 index after neoadjuvant chemotherapy in breast cancer. *Eur J Surg Oncol*. 2011 Feb;37(2):155–61.
- Tan QX, Qin QH, Yang WP, Mo QG, Wei CY. Prognostic value of Ki67 expression in HR-negative breast cancer before and after neoadjuvant chemotherapy. *Int J Clin Exp Pathol*. 2014 Sep;7(10):6862–70.
- Jones RL, Salter J, A'Hern R, Nerurkar A, Par-ton M, Reis-Filho JS, et al. The prognostic significance of Ki67 before and after neoadjuvant chemotherapy in breast cancer. *Breast Cancer Res Treat*. 2009 Jul;116(1):53–68.
- Li L, Han D, Wang X, Wang Q, Tian J, Yao J, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. *Future Oncol*. 2017 May;13(11):1021–34.
- Yoshioka T, Hosoda M, Yamamoto M, Taguchi K, Hatanaka KC, Takakuwa E, et al. Prognostic significance of pathologic complete response and Ki67 expression after neoadjuvant chemotherapy in breast cancer. *Breast Cancer*. 2015 Mar;22(2):185–91.
- Tange C, Kunisawa S, Maeda S, Shimozuma K. Cost-Effectiveness Analysis Of Pertuzumab For Metastatic Her2-Positive Breast Cancer In Japan. *Value Health*. 2015 Nov;18(7):A456–7.
- Diaby V, Ali AA, Williams KJ, Ezendu K, Soto-Perez-de-Celis E, Chavarri-Guerra Y, et al. Economic evaluation of sequencing strategies in HER2-positive metastatic breast cancer in Mexico: a contrast between public and private payer perspectives. *Breast Cancer Res Treat*. 2017 Dec;166(3):951–63.