Scholars LITERATURE

La Prensa Medica Argentina

Research Article

DOI: https://doi.org/10.47275/0032-745X-255
Volume 106 Issue 6

Assessment of Pathological Response to Neoadjuvant Chemotherapy in Breast Cancer

Malalah OH* and Al-Zubaidy AS

Department of Oncology, Oncology Teaching Hospital/National Cancer Center, Baghdad Medical City Complex, Iraq

Abstract

Neoadjuvant systemic therapy in the treatment of breast cancer was at first employed for patients with inoperable disease. Over the past years this treatment approach has been proved to be beneficial in many other clinical scenarios including those with early-stage, operable breast cancer. Neoadjuvant chemotherapy can reduce tumor burden and facilitating breast conservative surgery in selected patients without significant increase in local recurrence. The aim was to assess the pattern of pathological response in breast cancer patient in mastectomy specimens after treatment with neoadjuvant chemotherapy. Patients criteria in this study was patients with early stage or locally advanced breast cancer with or without axillary lymph node involvement and absence of distant metastasis, exposed to previous lumpectomy were excluded from the study. The patients were included from the outpatient consultation clinics in Oncology Teaching Hospital. History, physical examination, radiology and pathology reports were documented. The patients were categorized according to: The indication to neoadjuvant chemotherapy, the intrinsic subtypes (according to immunohistochemistry), and the pathological response. This retrospective study included 64 female patients with a mean age of 47.9±11.5 years. The largest group 32% in age range 45-54 years with overall p value < 0.001, the age was dependent factor for the response of tumor to neoadjuvant chemotherapy, the pCR occurred in about 28% of included patients, while non Pcr occurred in about 72% of our patients. HR+/Her 2-29.6% with pCR, 70.4% with non pCR, while HR+/Her2 16.7% with pCR, 83.3% with non pCR, Her2 enriched: 12.5% with pCR, 87.5% with non pCR and for Triple negative: 42.9% with pCR, 57.1% with non pCR, the P-value was 0.54. Regarding the pathologic residual tumor we get about 30% without pathologic residual tumor, 31.8% with residual ≤2 cm, 37.5% <2 cm with p-value 0.001. No major differences were found regarding the response of breast cancer to neoadjuvant chemotherapy in correlation to intrinsic subtype but the response to neoadjuvant chemotherapy is dependent to the age of the patients and their pretreatment tumor size.

Keywords: Neoadjuvant Chemotherapy; Breast Cancer; Preoperative Chemotherapy

Correspondence to: Ola H Malalah, Department of Oncology, Oncology Teaching Hospital/National Cancer Center, Baghdad Medical City Complex, Iraq; E-mail: medical research22@yahoo.com

Citation: Malalah OH, Al-Zubaidy AS (2020) Assessment of Pathological Response to Neoadjuvant Chemotherapy in Breast Cancer. Prensa Med Argent, Volume 106:6. 255. DOI: https://doi.org/10.47275/0032-745X-255.

Received: February 09, 2020; **Accepted:** April 30, 2020; **Published:** May 05, 2020

Introduction

The neoadjuvant (preoperative) approach to breast cancer is established as a therapeutic avenue for selected high-risk breast cancers, tumors ≥2 cm and for locally advanced (including initially ineligible for resection) disease [1]. The use of neoadjuvant therapy offers several clinical advantages. In patients with large tumors, the use of neoadjuvant therapy is likely to reduce the tumor size and can make patients candidates for surgical resection or can make some patients candidates for breast-conserving surgery rather than mastectomy. Because the primary tumor remains intact during therapy, the neoadjuvant approach allows for monitoring of treatment response and discontinuation of inactive therapy in the event of disease progression, thus saving the patient exposure to potentially toxic therapy [1,2]. Randomized clinical trials have found no significant differences in long term outcomes when systemic chemotherapy is given before or after surgery [3,4]. Historically, a primary advantage of administering preoperative systemic therapy has been to improve surgical outcomes [5]. Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy [4-6]. In addition, use of preoperative systemic therapy may provide important prognostic information based on response to therapy. Achieving a pathologic complete response (pCR) to neoadjuvant therapy is associated with favorable disease-free and overall survival (OS) in early-stage breast cancer. The correlation between pathologic response and long-term outcomes in patients with early-stage breast cancer is strongest for patients with triple- negative breast cancer, less so for HER2-positive disease, and least for hormone-positive disease [7-10]. According to the NCCN (National Comprehensive Cancer Network) Panel, among those with inoperable breast tumors, neoadjuvant systemic therapy is indicated in women with locally advanced or inoperable breast cancer including those with inflammatory breast cancer; those with N2 and N3 regional lymph node nodal disease; and T4 tumors. In patients

with operable breast cancer who are clear candidates for adjuvant chemotherapy, preoperative systemic therapy may be considered if a patient desires breast conserving surgery but the surgery is not possible due to the size of the tumor relative to that of the breast, with the hope that this will help obtain clear surgical margins at final resection [11]. Two studies (NSABP B-18 and NSABP B-27) have compared neoadjuvant chemotherapy to adjuvant chemotherapy using chemotherapy regimens of AC (doxorubicin+cyclophosfomide) alone or AC followed by docetaxel [9]. Both studies demonstrated superior DFS (disease free survival) and OS (overall survival) among the patients who achieved pCR compared with those who did not, although the pCR rate was only 13% to 26%. In the final analysis, however, there remained no difference in overall DFS or OS when the chemotherapy was administered in the neoadjuvant versus the adjuvant setting [10]. Although TNBC (triple negative breast cancer) is associated with a less favorable overall prognosis, this subtype of breast cancer is more chemo-sensitive and has a greater propensity of achieving a pCR to neoadjuvant chemotherapy compared with hormone receptor–positive disease [12,13]. Residual disease following neoadjuvant chemotherapy in TNBC and HER2- positive disease is associated with a worse DFS compared with other subtypes of breast cancer treated similarly. In this way, neoadjuvant chemotherapy can be used as a mechanism of evaluating tumor biology, disease resistance, and, ultimately, prognosis [14]. When neoadjuvant chemotherapy is used, the regimen selected should be the same as what would be administered in the adjuvant setting, typically consisting of an anthracycline and a taxanes [15]. In CALGB 40603study, the addition of neoadjuvant carboplatin to anthracycline and taxane-based chemotherapy was evaluated in patients with clinical stage II and III TNBC. Rates of pCR in the breast and axilla were 41% for standard chemotherapy and 54% when carboplatin was added to the regimen (p=0.0029) [16]. This significant improvement in pCR was also achieved when carboplatin was added to a more complex neoadjuvant anthracycline and taxane-based regimen in patients with TNBC (absolute increase of 20.8%) participating in the GeparSixto trial [17]. Despite encouraging results in a population in need of better therapies, there are no published data to define the efficacy of adjuvant carboplatin regarding its effect on important DFS and OS clinical outcomes [17]. The tumor response should be routinely assessed by clinical exam during the delivery of preoperative systemic therapy. Patients with operable breast cancer experiencing progression of disease while undergoing preoperative systemic therapy should be taken promptly to surgery. Imaging during preoperative systemic therapy should not be done routinely, but may be considered if tumor progression is suspected. Imaging prior to surgery should be determined by a multi-disciplinary team [10].

Patients and Methods

Design of the Study

This is a retrospective study that included patients who were evaluated in Oncology Teaching Hospital/Medical City, during period from April 1st 2018 to January 31st 2019. This study was approved by the scientific and ethical committee in Iraqi board of medical specialties in order to achieve its objective.

Study Population

The patients had been selected from the daily-visit patients to the consultation clinics of the Oncology Teaching Hospital. Each patient was reviewed and the data were collected and informed consents were obtained from all participants. All patients with locally advanced operable and non-operable breast cancer were included in this study after confirmation of the diagnosis by fine needle aspiration cytology (FNA) or core biopsy and exclusion of distant metastases by a routine metastatic workup including abdominal ultrasonography, bone scan, chest X-ray and computerized tomography.

Sample Collection

Prior to inclusion in this study, patients were assessed both clinically and by mammography to verify the tumor size and site and then the patients received type of neoadjuvant chemotherapy [NACT]. The doses and schedules of drug administration were modified according to-the drug toxicity evaluation before each single course. The response to NACT was assessed after surgery. The findings were correlated with the pretreatment and the preoperative clinical findings. We excluded patients who had one or more of the following criteria:

- Metastatic breast cancer
- Patient diagnosed by lumpectomy

Assessment of the Pathological Tumor Response

The histopathological evidence of the chemotherapeutic response was graded from the H&E sections on the basis of the parameters used in Miller-Payne criteria (MPC) for grading response of solid tumors to chemotherapy [18].

According to the (MPC) we have the following:

- pCR (pathological complete response): which is defined as the disappearance of all the tumor or DCIS in breast with no invasive carcinoma and negative lymph nodes.
- pPR (pathological partial response): which is defined as presence of invasive carcinoma with stromal alterations.
- pNR (pathological no response): which is defined as little modification in the original tumor appearance.

The invasive carcinomas and the lymph nodes were graded on the abovementioned criteria.

The patients were studied according to the following considerations: The indication to neoadjuvant chemotherapy. The intrinsic subtypes [HR±Her2- (ER+, PgR±Her2-), HR+/Her2+ (ER+, PgR±Her2+), Her2 enriched (ER-, PgR-/Her2+) and Triple negative(ER-, PgR-/Her2-)]. The pathological response [complete pathological response and no complete response.

The correlations among these groups and the pathological response had been accessed in the study.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Package for Social Sciences version 22). The response to treatment was found out expressed in number and tested by using test of proportions (Pearson's chi square test, Fischer's exact test and T test whichever was applicable). Statistical significance was considered whenever the P value was less than 0.05.

Results

Patient Demographics and Characteristics

Total of 50 female patients, diagnosed with breast cancer were recruited in this study, their age ranged from 25 to 71 years, with a

mean of 47.9 ± 11.5 years. The distribution of patients regarding Demographics and Characteristics summarized in the table 1.

In the current study the pCR in 28% of the patients while non pCR in 72% of them as showed in table 2, regarding the age most of the patients between 45-54 years as showed in table 2, p-value was <0.001 which was significant.

Indication of Neoadjuvant Chemotherapy

In the current study patients had been grouped into four categories according to the intrinsic subtypes, among HR±Her2-, HR±Her2+, Her2 enriched and Triple negative which was available in 48 patient's data only. The indications for neoadjuvant chemotherapy summarized in table 3.

Correlation of intrinsic subtypes of breast cancer with pathological response

Data about 48 patients in regards of the intrinsic subtype was available. The response of different intrinsic subtypes to neoadjuvant chemotherapy is summarized in table 4 which shows non- significant differences with p-value 0.54.

Correlation of clinical pretreatment tumor size (cT) stage with pathological residual tumor (ypT)

Data about cT was available in only 44 out of 50 patients and summarized in table 5 showing a p value of 0.001.

Discussion

This retrospective study included 50 female patients with a mean age of 47.9 ± 11.5 years, a population comparable to that included by other studies [19-26].

Table 1: Demographics and characteristic of the patients.

Patients		pCR	Non-pCR	Total
age	<45	11(61.1%)	7(38.9%)	18(36%)
	≥45	3(9.3%)	29(90.7%)	32(64%)
Histopathology	IDC	12(26.6%)	33(73.4%)	45(90%)
	Non-IDC	2(40%)	3(60%)	5(10%)
Hormonal state	+ve	9(27.2%)	24(72.8%)	33(68.7%)
	-ve	4(26.6%)	11(73.4%)	15(31.3%)
Her2 state	+ve	2(14.2%)	12(85.8%)	14(29.1%)
	-ve	11(32.3%)	23(67.7%)	34(70.9%)

Table 2: Distribution of patients regarding age and pathological response.

Patients age	pCR	Non-pCR	Total	P value
25-34	4(80%)	1(20%)	5(10%)	<0.001
35-44	7(54%)	6(46%)	13(26%)	
45-54	2(12.5%)	14(87.5%)	16(32%)	
55-64	1(10%)	10(90%)	11(22%)	
65-74	0	5(100%)	5(10%)	
Total	14(28%)	36(72%)	50(100%)	

Regarding the distribution of cases for age and the pathological response table 2: the largest group 32% in age range 45-54 years with overall p value <0.001 which was significant, the age was dependent factor for the response of tumor to neoadjuvant chemotherapy in similar with other studies: Loibl S, et al. (2014) [18], Keskin S, et al. (2011) [19] which was significant and in contrast to Chen XS, et al. (2010) [20], Li F, et al. (2018) [21] which was not significant. There was inverse relation older patient's response less to neoadjuvant chemotherapy as in Loibl S, et al. (2014) [18]. HR±Her2-: table 3 out of 27 HR±Her2- patients, 21 patients of were recruited for down staging for inoperable breast cancer where (77.7%) from HR+/Her2-. 4 Patients were recruited for breast conservation (14.8%) of HR±Her2-. As for inflammatory breast cancer 4 patients were assigned (7.5%) from HR±Her2-. As for total percentage for HR±Her2- about 56.3% that over result reported in Lee HJ, et al. (2014) [22] which was 47.3 %, 12.5% for Li F, et al. (2018) [21]. HR±Her2+: table 3, 6 patients HR±Her2+ patients, all of them were recruited for down staging for inoperable breast cancer. Whereas total percentage for HR±Her2+ about 12.5% that approximate to result reported in Hee Jin Lee et. al [19] which was 12.3% and less than that for Lee HJ, et al. (2014) [22] which was 56% Her2 enriched: table 3 out of 8 Her2 enriched patients, 5 patients of were recruited for down staging for inoperable breast cancer (62.5%) from Her2 enriched, one patient was recruited for breast conservation (12.5% of Her2 enriched) and for inflammatory breast cancer, 2 patients were assigned (25% of Her2 enriched). Whereas total percentage for Her2 enriched about 16.6 % that slightly over result reported in Hee Jin Lee et. al [19] which was 13.4% and 17.4% for Fang Li et al [23].

Triple Negative: table 3 out of 7 of triple negative patients, 7 patients for down staging for inoperable breast cancer were recruited (100%) from triple negative, whereas total percentage for triple negative about 14.6% that below result reported in Lee HJ, et al. (2014) [22] which was 27 % and slightly more than that for Li F, et al. (2018) [21] 13.6% In this study table 4 pCR occurred in about 27.1% of included patients compared to 7.9% reported by El-Didi MH, et al. (2000) [23], 16.2% for Li F, et al. (2018) [21].

HR±HER-: Table 3 and table 4 (29.6%) of patients with pCR, (70.4%) of patients with non pCR while. While HR±HER+: (16.7%) of patient with pCR, (83.3%) patients with non pCR. Her2 enriched: (12.5%) of patient with pCR, (87.5%) patients with non pCR. As for Triple negative: (42.9%) of patients with pCR, (57.1%) of patients with non pCR.

The P-value was 0.54 which was not significant the response of tumor to neoadjuvant chemotherapy was not dependent on the intrinsic subtypes of treatment in contrast to Lee HJ, et al. (2014) [22], Li F, et al. (2018) [21], Goldstein NS, et al. (2007) [24], Chen XS, et al, (2010) [21], Prat A, et al. (2015) [25] which was significant.

According to cT stage and ypT table 5 cT1: 6 patients (13.6%) were recruited, 4(66.7%) of them became ypT0 while 2(33.4%) of them still ypT1. cT2:10(22.7%) patients were recruited, 5(50%) of them became ypT0, 4(40%) of them became ypT1 while one(10%) patient still with

Table 3: Shows Distribution of intrinsic subtype categories and the indication for neoadjuvant treatment.

Indication for Chemotherapy	HR±Her2- No.(%)	HR±Her2+ No.(%)	Her2 enriched No.(%)	Triple negative No.(%)	Total
Down staging For inoperable	21(77.7)	6(100)	5(62.5)	7(100)	39(81.3)
Breast conservative surgery	4(14.8)	0	1(12.5)	0	5(10.4)
Inflammatory	2(7.5)	0	2(25)	0	4(8.3)
Total	27(56.3)	6(12.5)	8(16.6)	7(14.6)	48(100)

Table 4: Response of breast cancer to neoadjuvant chemotherapy.

Intrinsic subtype	pCR	non pCR	Total	p value
HR±Her2-	8(29.6%)	19(70.4%)	27(56.5%)	0.54
HR±Her2+	1(16.7%)	5(83.3%)	6(12.5%)	
Her2 enriched	1(12.5%)	7(87.5%)	8(14.5%)	
Triple -ve	3(42.9%)	4(57.1%)	7(14.5%)	
Total	13(27.1%)	35(72.9%)	48(100%)	

Table 5: Pathological residual tumor (ypT) in different clinical pretreatment tumor size (cT) stage.

cT stage	ypT age						P value
	0	1	2	3	4	Total	
	No.(%)	No.(%)	No.(%)	No.(%)	No.(%)		
1	4(66.7)	2(33.4)	0	0	0	6(13.6)	**0.001**
2	5(50)	4(40)	1(10%)	0	0	10(22.7)	
3	0	4(44.4)	3(33.3)	2(22.2)	0	9(20.4)	
4	4(21.1)	4(21.1)	6(31.6)	3(15.8)	2(10.5)	19(43.3)	
Total	13(29.5)	14(31.8)	10(22.7)	5(11.3)	2(4.5)	44(100)	

cT: clinical tumor state; **ypT:** pathological residual tumor

ypT2. cT3:9(20.4%) patients were recruited, no one of them became ypT0, 4(44.4%) of them became ypT1, 3(33.3%) of them became ypT2 while 2(22.2%) of them still with ypT3. cT4:19(43.3%) patients were recruited, 4(21.1%) of them became ypT0, 4(21.1%) of them became ypT1, 6(31.6%) of them became ypT2, 3(15.8%)of them became ypT3 while 2(10.5%) of them still with ypT4.

Regarding the correlation p-value was 0.001 which was significant; the response of tumor to neoadjuvant chemotherapy is dependent to the pretreatment size of the tumor similar to Lee HJ, et al. (2014) [22], Li F, et al. (2018) [21] and in contrast to Chen XS, et al. (2010) [20] which not significant. The difference in intrinsic subtypes response to neoadjuvant chemotherapy may attributed to difference in number of patients whom included in the different studies and racially difference (64 in our study in contrast to 351 for Lee HJ, et al. (2014) [22] Korean study, 264 for Li F, et al. (2018) [21] Chinese study, 68 for Goldstein NS, et al. (2007) [24], American study , 560 for Chen XS, et al. (2010) [20] Chinese study, 38 for El-Didi MH, et al. (2000) [23] Egyptian study).

Conclusion

In conclusion, no major differences were found regarding the response of breast cancer to neoadjuvant chemotherapy in correlation to intrinsic subtype but the response to neoadjuvant chemotherapy is dependent to the age of the patients and their pretreatment tumor size (elderly patient's response less to chemotherapy and small size tumor response better).

References

1. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, et al. (1999) Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 17:4 60-469.
2. Guarneri V, Broglio K, Kau SW, Cristofanilli M, Buzdar AU, et al. (2006) Prognostic value of pathological complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol 24: 1037-1044.
3. Mauri D, Pavlidis N, Ioannidis JP (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 97: 188-194.
4. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, et al. (2008) Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol 26: 778-785.
5. Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, et al. (2008) Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol 26: 814-819.
6. Killelea BK, Yang VQ, Mougalian S, Horowitz NR, Pusztai L, et al. (2015) Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. J Am Coll Surg 220: 1063-1069.
7. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26: 1275-1281.
8. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, et al. (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384: 164-172.
9. Von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, et al. (2012) Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30: 1796-1804.
10. Carey LA, Metzger R, Dees EC, Collichio F, Sartor CI, et al. (2005) American Joint Committee on Cancer tumor-node-metastasis stage after neoadjuvant chemotherapy and breast cancer outcome. J Natl Cancer Inst 97: 1137-1142.
11. National Comprehensive Cancer Network (2018) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.
12. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13: 2329-2334.
13. Haddad TC, Goetz MP (2015) Landscape of neoadjuvant therapy for breast cancer. Ann Surg Oncol 22: 1408-1415.
14. Earl HM, Vallier AL, Hiller L, Fenwick N, Young J, et al. (2014) Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an openlabel, 2x2 factorial randomised phase 3 trial. Lancet Oncol 15: 201-212.
15. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-perweek paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 33: 13-21.
16. Von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, et al. (2014) Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 15: 747-756.
17. Mukherjee P, Sharma S, Sheikh ZA, Vijaykumar DK (2014) Correlation of clinico-pathologic and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer. Indian J Cancer 51: 25-29.
18. Loibl S, von Minckwitz G, Untch M, Denkert C (2014) Predictive factors for response to neoadjuvant therapy in breast cancer. Oncol Res Treat 37: 563-568.
19. Keskin S, Muslumanoglu M, Saip P, Karanlık H, Guveli M, et al. (2011) Clinical and pathological features of breast cancer associated with the pathological complete response to anthracycline-based neoadjuvant chemotherapy. Oncology 81: 30-38.

20. Chen XS, Wu JY, Huang OU, Chen CM, Wu J, et al. (2010) Molecular subtype can predict the response and outcome of Chinese locally advanced breast cancer patients treated with preoperative therapy. Oncol Rep 23: 1213-1220.

21. Li F, Ma L, Geng C, Liu C, Deng H, et al. (2018) Analysis of the relevance between molecular subtypes and efficacy of neoadjuvant chemotherapy in breast cancer as well as its prognostic factors. Pathol Res Pract 215: 338-344.

22. Lee HJ, Song IH, Seo AN, Lim B, Kim JY, et al. (2014) Correlations between molecular subtypes and pathologic response patterns of breast cancers after neoadjuvant chemotherapy. Ann Surg Oncol 22: 392-400.

23. El-Didi MH, Moneer MM, Khaled HM, Makarem S (2000) Pathological assessment of the response of locally advanced breast cancer to neoadjuvant chemotherapy and its implications for surgical management. Surg Today 30: 249-254.

24. Goldstein NS, Decker D, Severson D, Schell S, Vicini F, et al. (2007) Molecular classification system identifies invasive breast carcinoma patients who are most likely and those who are least likely to achieve a complete pathologic response after neoadjuvant chemotherapy. Cancer 110: 1687-1696.

25. Prat A, Fan C, Fernández A, Hoadley KA, Martinello R, et al. (2015) Response and survival of breast cancer intrinsic subtypes following multi-agent neoadjuvant chemotherapy. BMC Med 13: 303.